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Synthetic approaches to cis,cis -1-aza-1,5-cyclo-octadiene ; Synthetic approaches to cis -0-bisabolene.

Pierre M. Beaumier
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PART I

SYNTHETIC APPROACHES TO CIS, CIS-1-AZA-1,5-CYCLOOCTADIENE

PART II

SYNTHETIC APPROACHES TO CIS- γ -BISBOLENE

BY

PIERRE M. BEAUMIER

A Dissertation

Submitted to the Faculty of Graduate Studies through the
Department of Chemistry in Partial Fulfillment
of the Requirements for the Degree of
Doctor of Philosophy at the
University of Windsor

Windsor, Ontario

1974

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515357

To Colleen and Stéphanie

ABSTRACT

PART I

Three synthetic pathways to 1-aza-1,5-cyclooctadiene via a 4-substituted 1-azabicyclooctane intermediate, were investigated. Attempts to obtain the appropriately substituted bicyclooctane by a polyphosphoric acid cyclization of 2-(2-pyrrole) propionic acid did not materialize.

The alkylation of thallium(I) salts of 1,3-cyclopentanedione and 1,3-cyclohexanedione was studied in detail in an attempt to obtain synthetically useful C-alkylated intermediates. However, the salts showed a preference for O-alkylation, with very little C-alkylation.

A study of the Diels Alder reaction between 1,1-diethoxycyclopentadiene and several dienophiles was undertaken. The Diels Alder adduct between the diene and ethylazodicarboxylate was reduced, and treatment with aqueous potassium hydroxide produced an azo intermediate which was reduced catalytically to 2,5-diamino-1,1-diethoxycyclopentane. The amine groups were functionalized and the ketal hydrolyzed to the ketone. The cyclization of this ketone to the azabicyclooctane was accomplished by reacting the latter with vinyltriphenylphosphonium bromide.

PART II

The synthesis of cis- γ -bisabolene was attempted via a Wittig reaction between the phosphorane derived from 4-chlorocyclohexyl ethylene ketal (8) and 5, 5-dimethoxy-2-pentanone (9). Because of difficulties in preparing the phosphonium salt of the chlorocyclohexyl system, this approach was abandoned.

The Grignard reaction between 9 and 8 was successful, but low yields were obtained, which made completion of the project impossible.

ACKNOWLEDGEMENTS

I would like to take the opportunity to thank Dr. J. M. McIntosh, whose continued aid, encouragement, guidance and patience made this work possible.

I would also like to thank my wife Colleen for her support and encouragement. Thanks also goes to Mrs. Gail Doyle for typing work on this manuscript.

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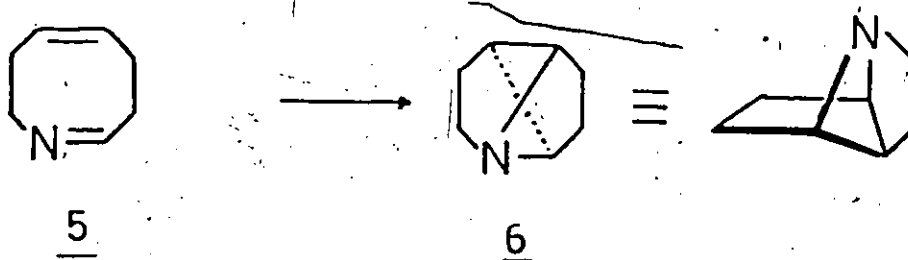
PART I

SYNTHETIC APPROACHES TO CIS, CIS-1-AZA-1,5-CYCLOOCTADIENE

INTRODUCTION

In recent years there have been several studies on the photochemistry of 1,5-cyclooctadiene (1)¹⁻⁴. Initially Srinivasan¹ found that the major product when irradiating cis,cis-1,5-cyclooctadiene copper complex was tricyclo-[3.3.0.0.^{2,6}]octane (2) along with a variety of other products (Fig.1). The mechanism of the reaction is still unclear but the isolation⁴ of cis,trans and trans,trans-1,5-cyclooctadiene (3) and (4) from the copper complex suggests that the latter (4) may be an intermediate. There have also been interesting thermal rearrangements of 1, using Nickel catalysts⁵, to form bicyclo[3.3.0]octene in high yield (>90%).

These novel conversions led to our attempts to synthesize and study the nitrogen analogue cis,cis-1-aza-1,5-cyclooctadiene (5). The latter under photochemical reaction conditions should produce 6 if the reaction proceeds in the



same manner as the carbocyclic analogue. The properties

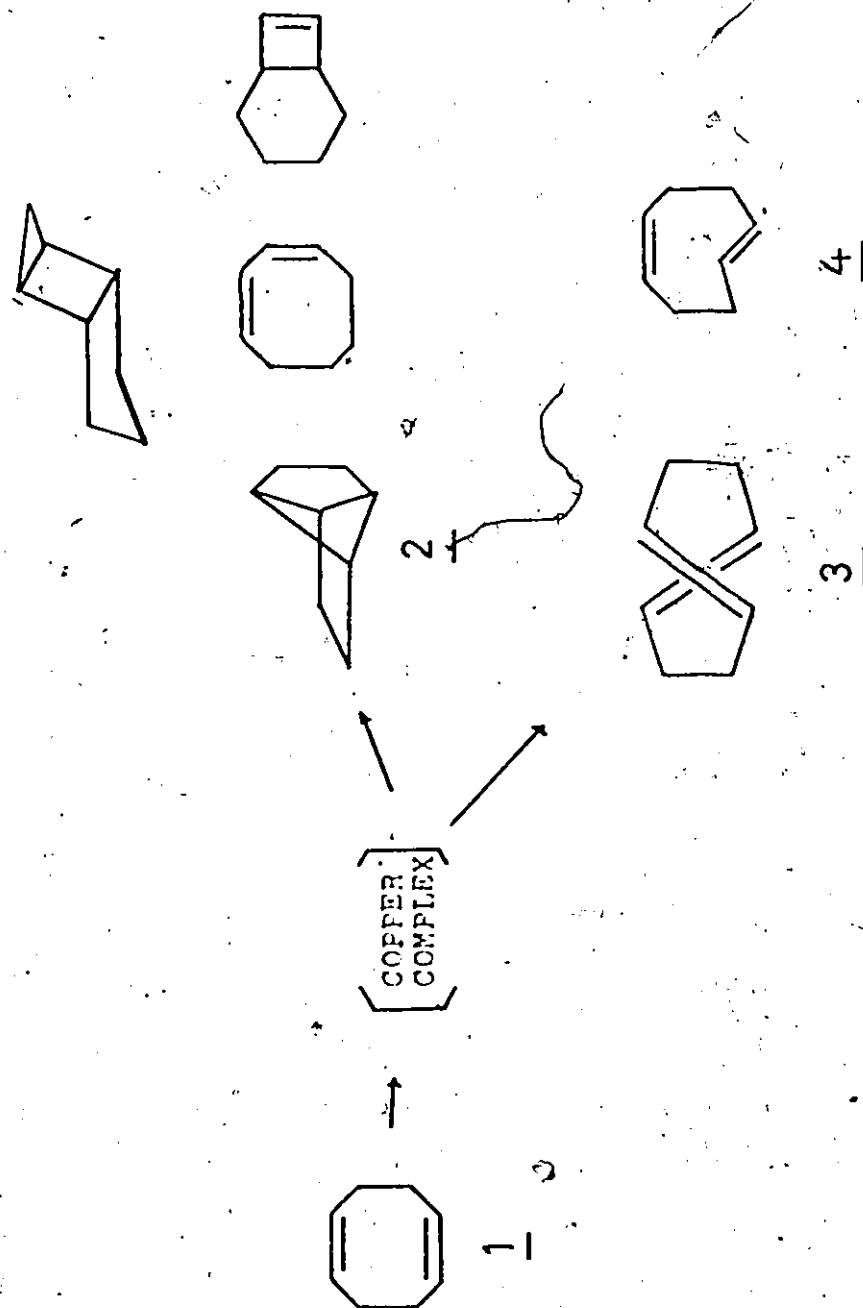
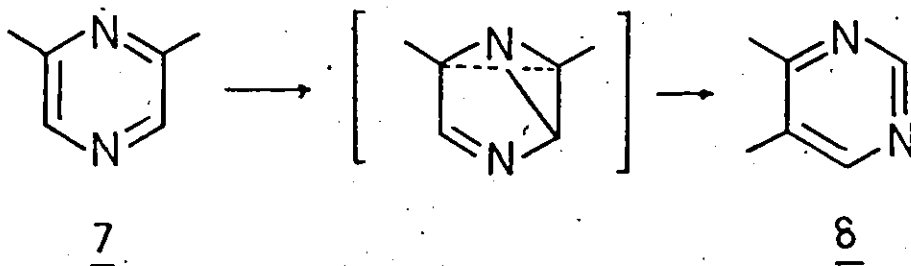


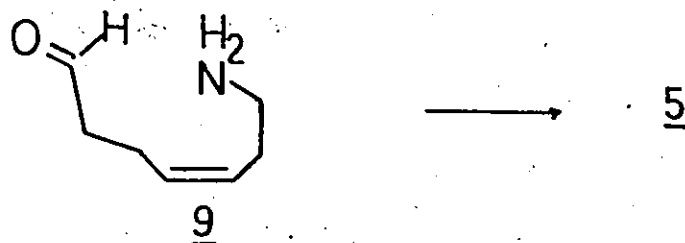
FIG. 1 Photochemical products of 1,5-cyclooctadiene

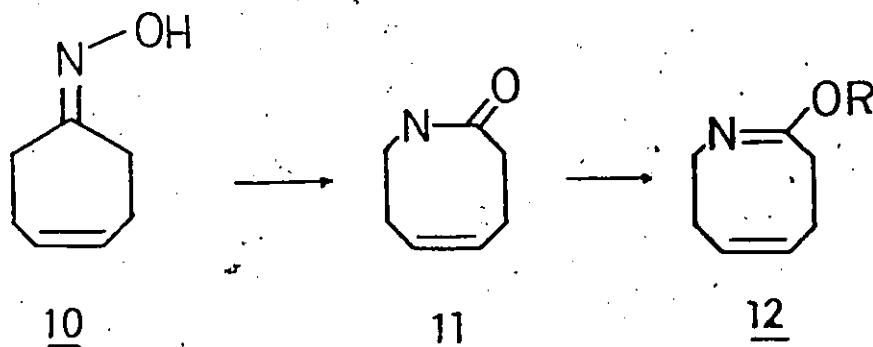
of 6 interested us, especially its basicity because of the strained ring network which pulls back on the nitrogen atom leaving a protruding electron pair.

Although little work has been done on imine photochemistry⁷, the formation of 4,5 dimethylpyrimidine (8) on photolysis of 2,6-dimethylpyrazine (7)⁶ via a crossover intermediate supports the anticipated rearrangement of 5 to 6.



There are several ways to approach the synthesis of 5, the most direct being an intramolecular cyclization of 7-amino-4-heptenal (9). Although this route seems facile, difficulty in closing a medium-sized ring by a reversible hemiaminal intermediate makes this approach unattractive. The ring expansion (Beckmann rearrangement)





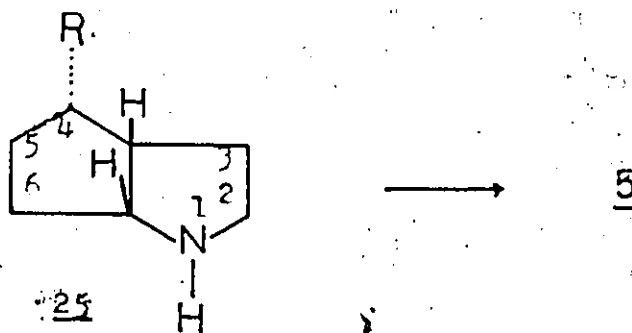
of 10 to give the lactam 11 which could be converted to the imine 12 was attempted previously. However synthesis of 4-cyclohepteneone, precursor of the oxime 10, caused difficulties and the reaction scheme was abandoned⁸.

A general approach to making medium-sized ring systems is the fragmentation of bicyclic precursors. A detailed study of this type of reaction was carried out by Grob⁹ who examined the solvolytic fragmentation of a number of decahydroquinoline derivatives. His findings illustrated the importance of stereoelectronic factors in these fragmentation reactions. The conformational representations depicted in Fig. 2 show that both the trans, anti-isomer 13 and the cis, syn-isomer 15 can achieve a trans, antiparallel alignment of the central carbon-carbon bond and the carbon-oxygen bond of the tosylate grouping. This allows continuous overlap of adjacent rehybridizing sp^3 orbitals in the

transition states 13a and 15a. The trans,syn-isomer 17 does not allow this orbital overlap and elimination takes place to give the product 18.

This type of fragmentation is not limited to heterocyclic compounds. It has been used in a synthesis of caryophyllene¹⁰ in which the fragmentation of alcohols 19 and 21 produced the cyclononones 20 and 22. Marshall¹¹ has also used this reaction to make the cyclodecadiene 24 from the precursor 23. (Fig. 2b)

From the data available on ring fragmentations it was felt that this was the most promising approach to the synthesis of 5. The necessary intermediate would be cis,syn-1-azabicyclo[3.3.0]octane 25* with a suitable leaving group at the 4 position. The synthesis of the unsubstituted



system has been accomplished by three pathways (Fig. 3).

* This compound is also referred to as octahydrocyclopenta[b]pyrrole.

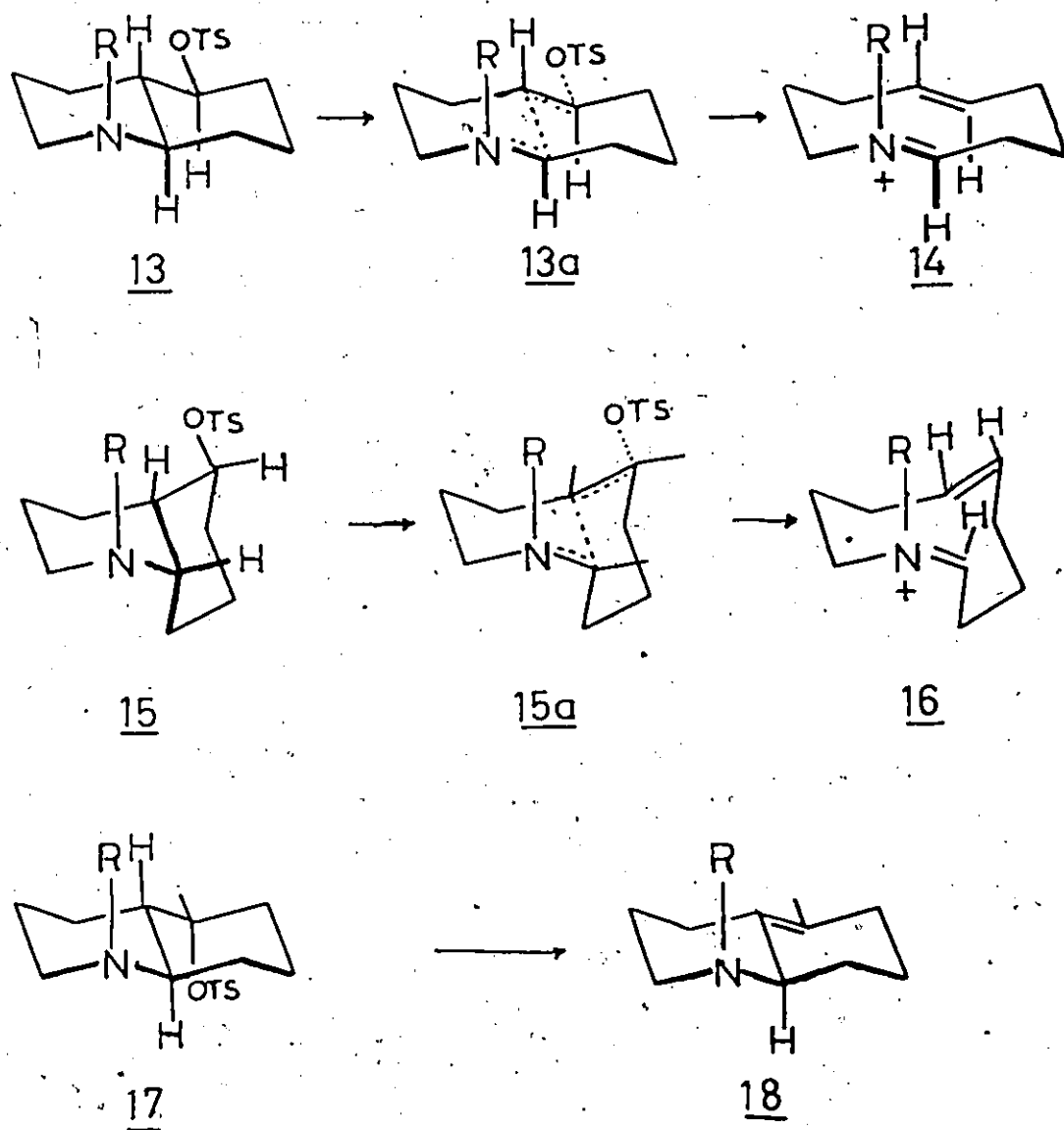


FIG-2a Fragmentation of decahydroquinoline derivatives 9.63

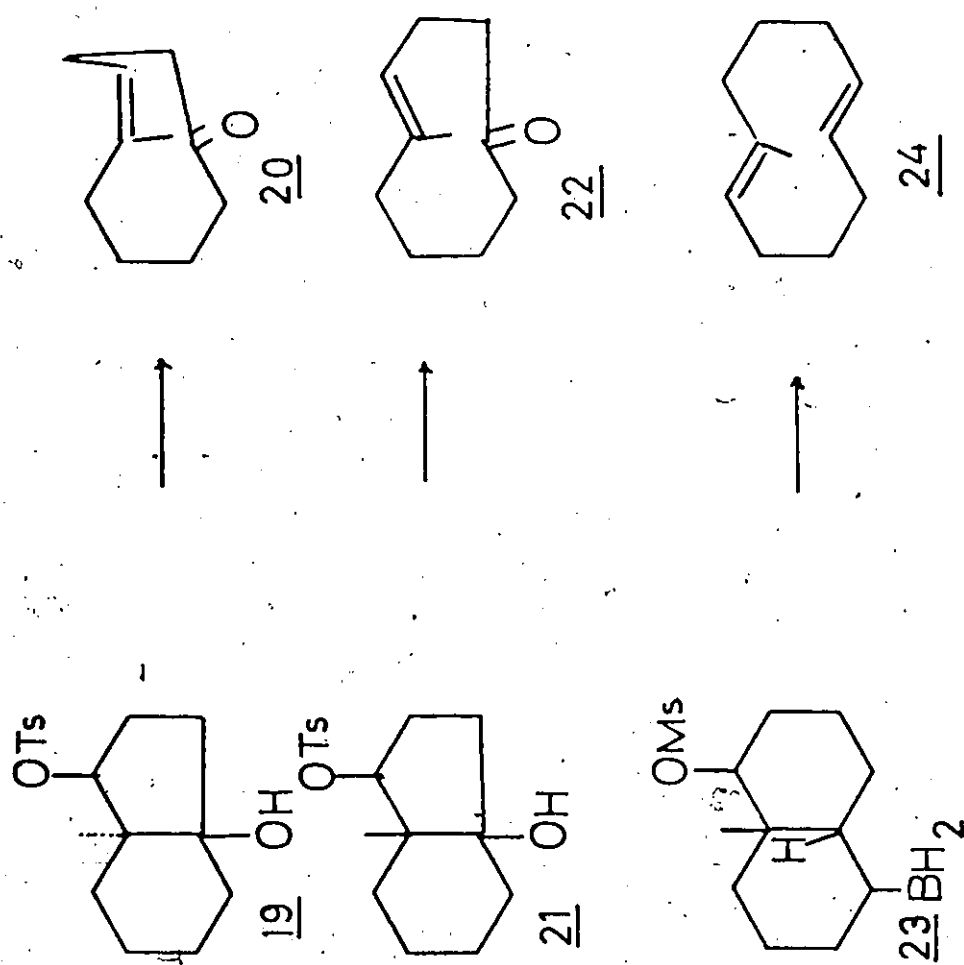


FIG. 2b Bicyclic ring fragmentations

The first of these (Fig.3,eq.1) is a Hofmann-Loeffler Freytag reaction which produced the cis-fused ring system in 20% yields¹². The second method (eq.2) consists of an intramolecular nucleophilic displacement on a substituted cyclopentylamine¹³. The stereochemistry of the product obtained, depends on the relationship between the amine and sidechain. Reduction of the oxime which is the amine precursor gave only 22% of the required cis-amine. The third method (eq.3) is a polyphosphoric acid cyclization of a 2-pyrrole propionic acid to form the bicyclic product in 51% yield.

Of these three methods, the third one is the only one to give a reasonable yield and a functional group in the 4-position. The starting materials necessary to obtain this substitution by the other two methods are complex and difficult to synthesize.

Hence the third method was adopted as the most promising approach to 25.

RESULTS AND DISCUSSION

The results and discussion have been grouped by attempted synthetic schemes.

2-Pyrrolepropionic Acid Cyclization

The diagram in Fig.4 outlines the first scheme proposed for the synthesis of the 2-azabicyclo[3.3.0]octane system 25. The polyphosphoric acid cyclization of 30 would produce

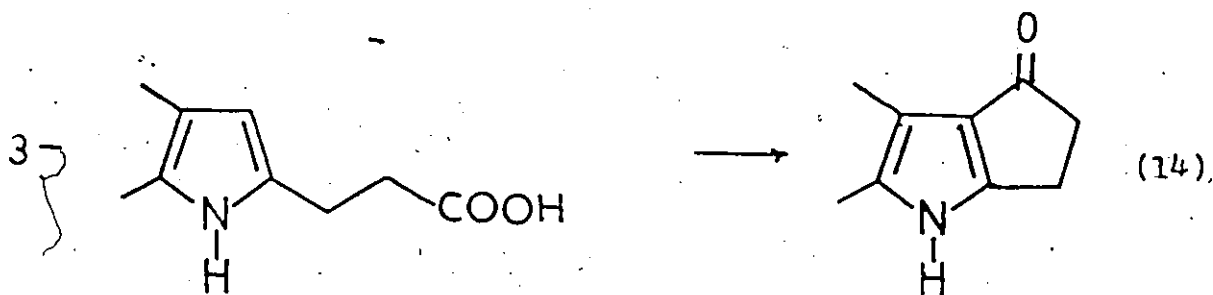
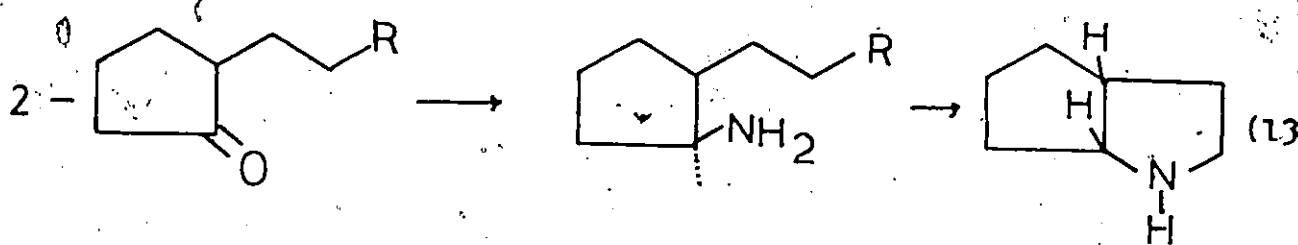
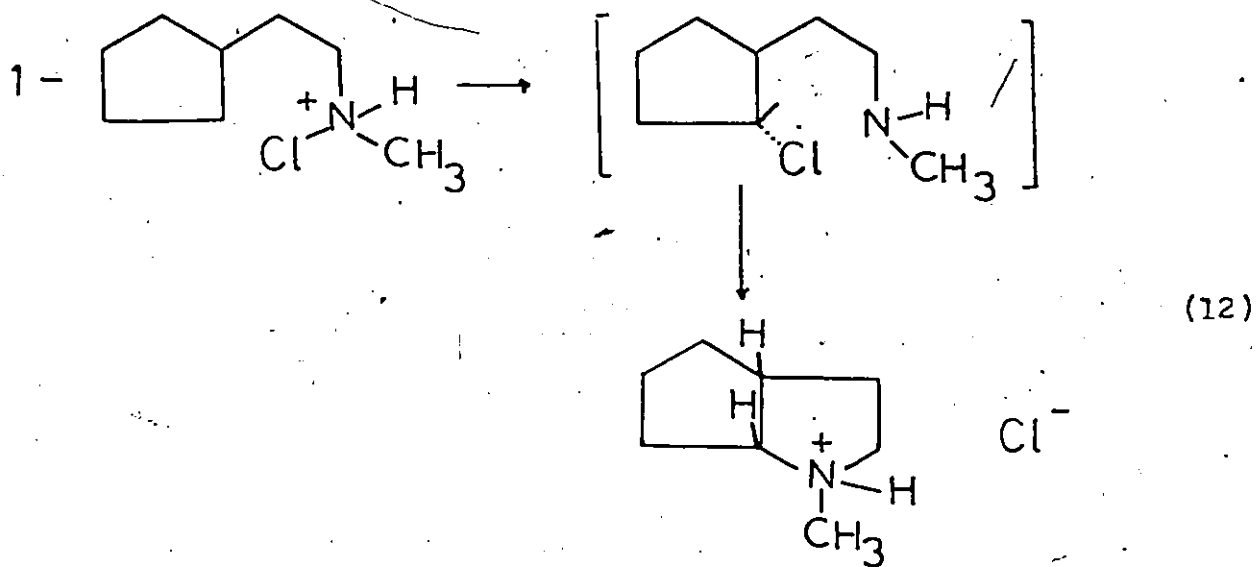


FIG.3 Pathways to 1-azabicyclo[3.3.0]octane

the bicyclic frame 32 with a substituent in the desired position. Reduction of 32 should give the desired product. It was recognized that a mixture of alcohols might be obtained but oxidation to the ketone and a selective reduction from the least hindered side seemed feasible.

Pyrrole (26) was converted to 2-pyrrolealdehyde (27), in good yield, according to an established procedure¹⁵. The Wittig reaction between the phosphorane 28 and 27 had previously been studied¹⁶ in detail, because of the expected reduced carbonyl character of the aldehyde¹⁷ 27. The reaction proceeded in moderate yield (60-65%) to give only the trans isomer 29. This was anticipated since phosphoranes with electron withdrawing groups are known to give only trans isomers¹⁸. Purification of 29 by gas-liquid chromatography (glc) effected isomerization to the cis isomer 29a. This conversion was interesting since cis isomers usually have the higher energy, owing to steric effects. Attempts to isomerize 29 to 29a by heating in triglyme or neat to 200° and 250°C respectively were unsuccessful. Acidic impurities on the glc column were assumed to be responsible for this conversion. The reason for the cis preference was found to be a coordination between the pyrrole nitrogen atom and the positively polarized carbonyl carbon atom. This manifested itself as a carbonyl frequency shift from 1704cm⁻¹ in 29 to 1690cm⁻¹

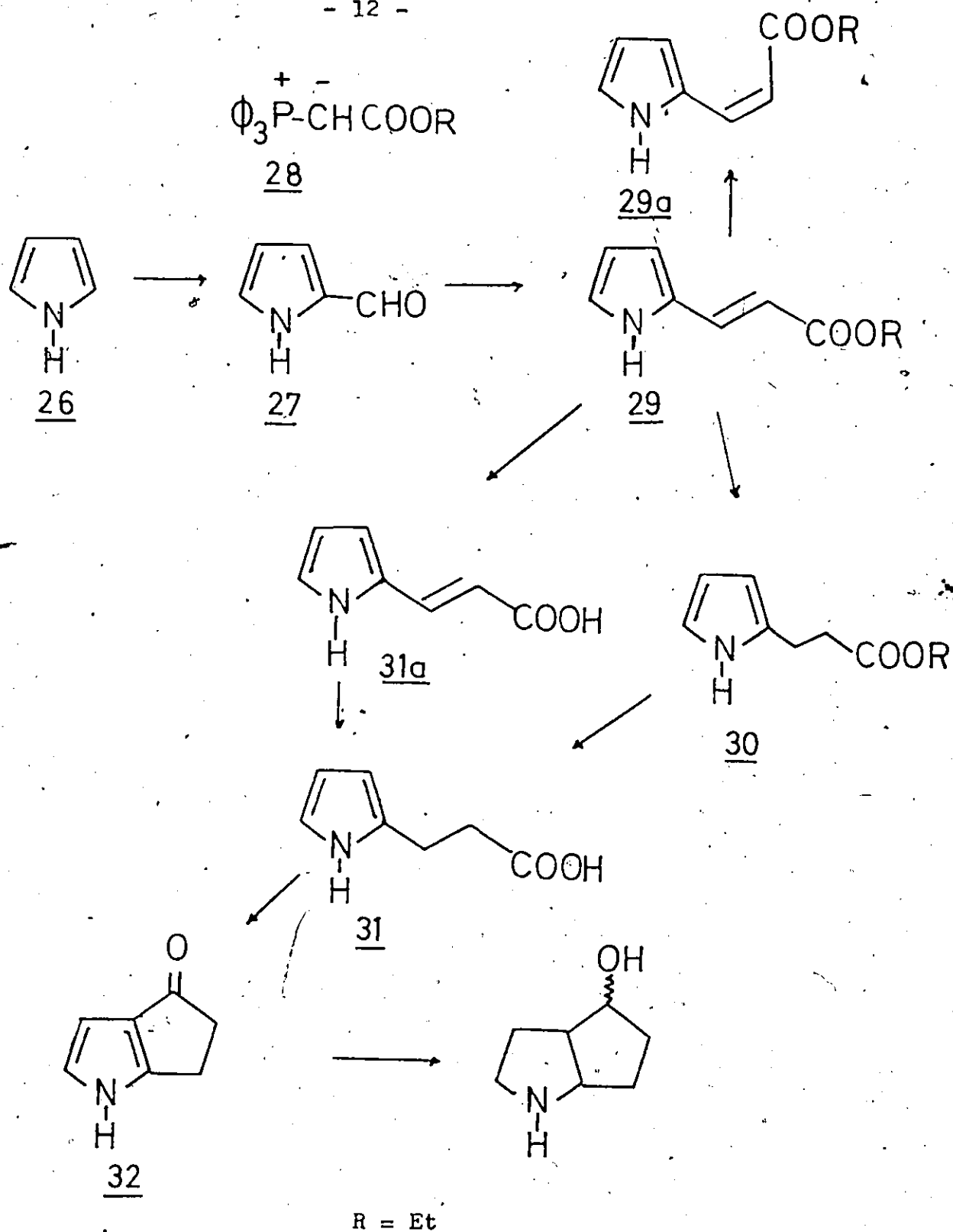


FIG. 4 Proposed synthetic scheme via pyrrole

in 29a, and the N-H stretching frequency whose intensity was decreased substantially and shifted 70cm^{-1} . Reduction of 29 with palladium on charcoal produced 30 in good yield. Saponification of the ester 30 with KOH/H₂O did not produce 31. The major product was a high melting solid (245°) which could not be characterized. Various reaction conditions for the conversion of 30 to 31 were attempted unsuccessfully. The ester 29 was converted to the acid 31a, which was easily reduced to the desired 31. However, several attempts to reproduce this reaction on a larger scale, failed. A low yield for the formation of 32 was anticipated because of the sensitivity of pyrrole rings to acidic media¹⁹. Hence, it was necessary to obtain 31 in good yield. Since we were unable to complete the reaction sequence, a different approach was adopted.

1,3-Cyclopentanedione Alkylation

Substitution of 1,3-cyclopentanedione (35) with an appropriate fragment could be a method of obtaining the desired skeleton 34 as outlined in Fig. 5. Although

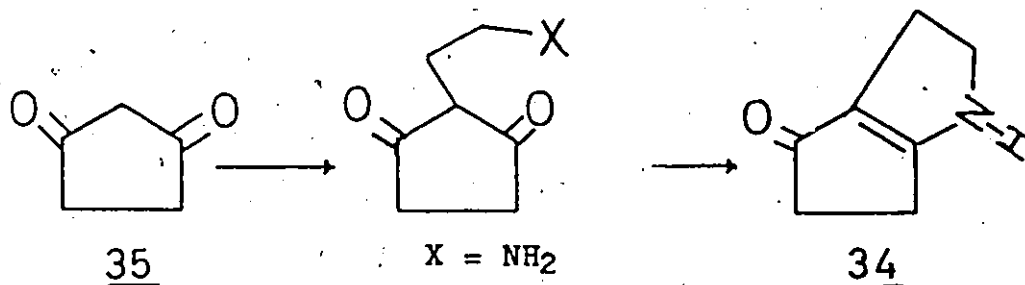
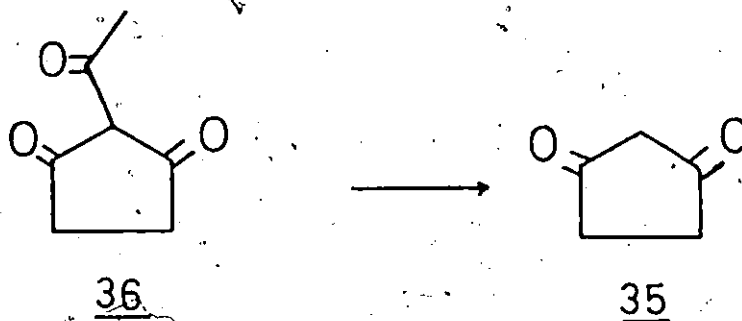


FIG. 5 Cyclization of alkylated 1,3-cyclopentanedione
 cyclopentanedione and its alkylated derivatives have been

used in the synthesis of many materials of varying degrees of complexity²⁰, methods for its preparation, particularly on a large scale, are limited. The dione 35 has been prepared from the cyclization of ethylmethyl- β -keto adipate, but the reported yield was unacceptable (7.5%)²¹. The hydrolysis of the trione 36 has been reported²². The trione was prepared in low yield according to the reported procedure and the hydrolysis attempted. Unfortunately no dione 35



could be isolated.

Catalytic hydrogenation over platinum and zinc acetic acid reduction of 4-cyclopentene-1,3-dione 37 had been previously reported²³. Low yields of 35 were obtained, but the choice of catalyst and reaction conditions for these reactions did not appear to be optimal. Thus a detailed investigation of the procedures was undertaken.

DePuy²³ carried out the reduction of 37 with Adam's catalyst (Fig.6) and found 2.7 molar equivalents of H₂

absorbed without any appreciable break in hydrogen uptake. Less than 2% of the dione 35 was produced. Equal amounts of cyclopentanone (41) and 3-hydroxycyclopentanone (40) were formed and accounted for the majority of the products. The proposed reaction sequence²³ follows an initial reduction of a carbonyl group to produce 38 which then undergoes further reduction.

It is well established that selective hydrogenation of olefins in the presence of carbonyl function occurs better with palladium rather than platinum catalyst.²⁴

Therefore we carried out the reduction of 37 with palladium and found that in contrast to the results using platinum, no 41 was formed. The major product was the desired dione 35 accompanied by a large amount of 40. Variation of the solvent from 95% to 75% ethanol drastically reduced the rate of reduction but did not change the product distribution substantially.

The reduction of conjugated diketones with zinc in acetic acid is a well documented process²⁵, but the reported yields^{23,26} of 35 from the reduction of 37 were low. These results were verified using the reported procedures.

However it was found that activating the zinc²⁷ prior to use improved the yields to a point where dione 35 could easily be prepared in large quantities. Subsequently another report²⁸ on the reduction of 37 has appeared in

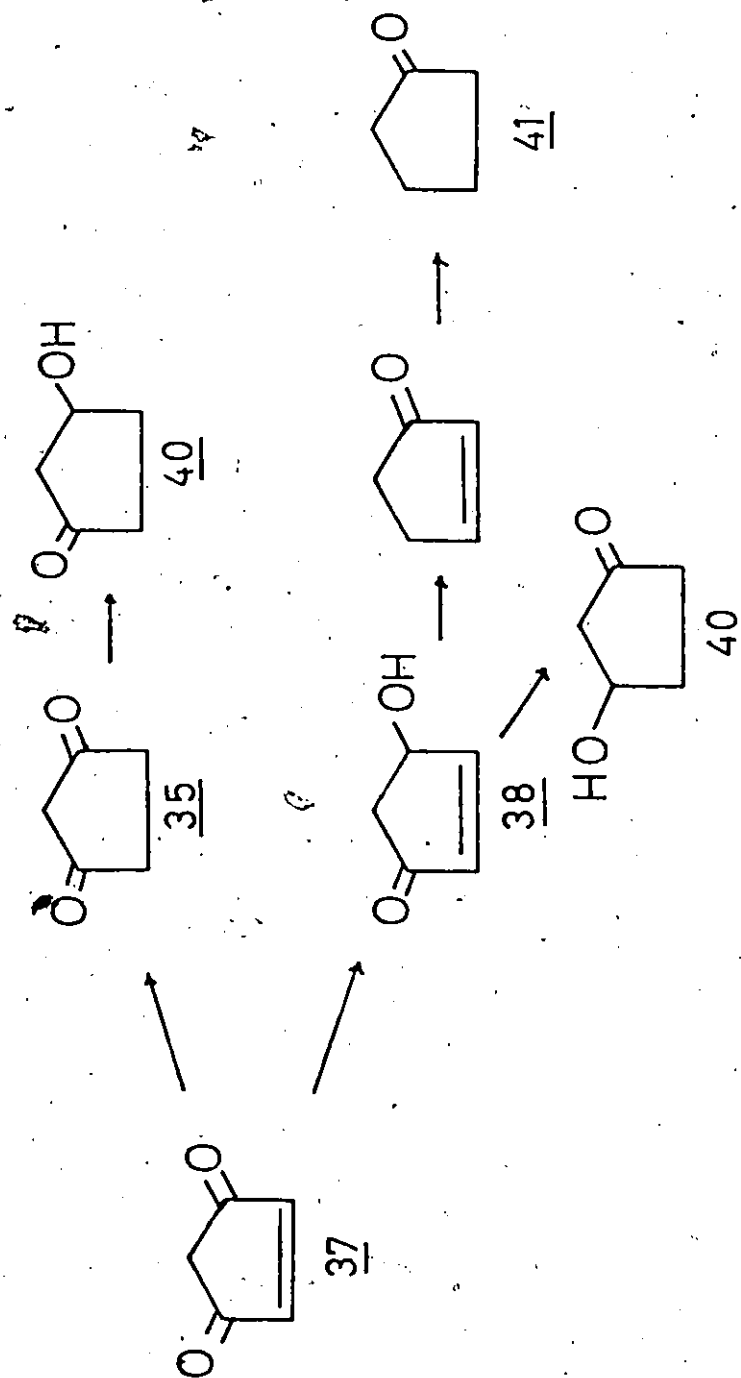


Fig. 6 Reduction of 4-cyclopentene-1,3-dione.

which the latter was reduced quantitatively to 35 by means of a rhodium (III) homogeneous catalyst.

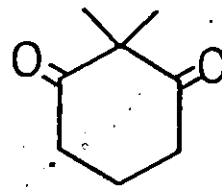
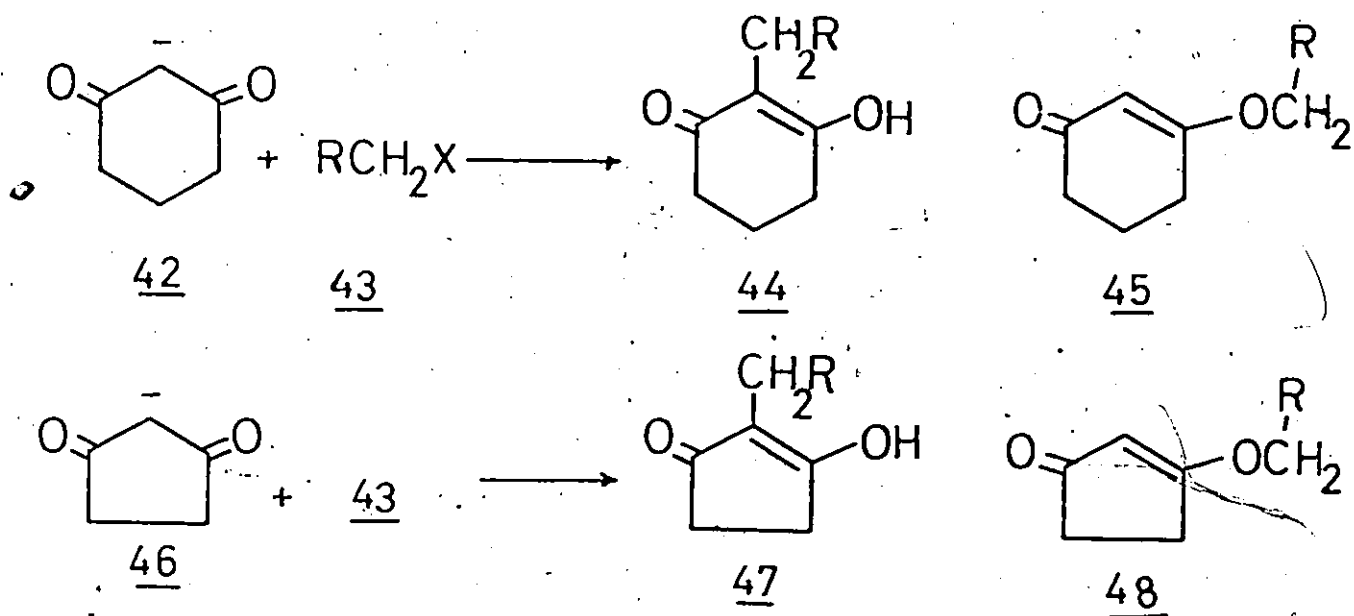
Regiospecific C-alkylation or acylation of 1,3-diketones can be extremely difficult (for an excellent summary of the problems, see ref.29). The sodium or potassium salts usually give mixtures of C- and O-alkylation, accompanied by some dialkylated products^{30,31}. However it has recently been reported³² that thallium (I) salts of 1,3-diketones give regiospecific C-alkylation and acylation. The reactions were carried out with thallium salts of acyclic diketones as heterogeneous mixtures, the halides being the solvent. A crystal structure study of the salts showed that the thallium and oxygen atoms were inside the crystal, exposing only the carbon skeleton to the action of the alkylating agent. The reaction was said to occur at the crystal surface, literally "peeling away" layer after layer. Retention of the geometry of the thallium chelate in the transition state leads to "regiospecificity rivaling that of an enzymatic reaction"³².

There has been no report of the alkylation of cyclic 1,3-diketones using this method. The sodium and potassium salts of cyclic diketones afford mixtures of carbon and oxygen alkylated products^{33,34}. Thus a detailed study of the alkylation of cyclic thallium salts was undertaken in an attempt to prepare C-alkylated diketones as precursors

to 25.

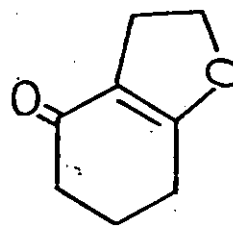
The salts 42 and 46 were prepared by adding thallium ethoxide to an ethanolic benzene solution of the appropriate diketone. Initially the reaction of 42 and 46 with methyl iodide (43a) and ethyl bromide (43b) was studied. The results, especially with 43b, in terms of C-alkylation were disappointing (Table 1). However, since most of the charge on the ambident ion will reside on the oxygen atom, an initial coordination of one of the two positively polarized atoms in bifunctional molecules such as 43(c,d,e,f) might orient it towards the α -carbon atom of the diketone, thus improving the chance for C-alkylation. The products from such a reaction would lend themselves to the preparation of the desired 25. The results obtained are summarized in Fig.7 and Table 1. All the reactions were carried out as heterogeneous mixtures with the salts as suspensions in the alkylating agents which also served as solvent.

The isolation of a 13% yield of 4-oxo-2,3,4,5,6,7 -hexahydrobenzofuran (50) from the reaction of 42 and ethylene dibromide (43c) indicated the occurrence of some C-alkylation and gave some support to our hopes for improved yields of 44 from bifunctional alkylating agents. However, when 42 was treated with methyl bromoacetate (43d) or ethyl chloroacetate (43f) complex mixtures resulted, from which could be isolated the ethers 45d and 45f. The remainder of the



49

- a X=I, R=H
- b X=Br, R=CH₃
- c X=Br, R=CH₂Br
- d X=Br, R=COOMe
- e X=Br, R=COOEt
- f X=Cl, R=COOEt



50

FIG. 7 Alkylation products of salts 42 and 46

TABLE 1

Products and Yields from Alkylations of Salts 42 and 46

Run No.	Reactants	Catalyst	Temp.	% Conversion	% O-alkylation	% C-alkylation	% other
1	<u>42</u> + <u>43a</u>	--	41	92	22 (<u>45a</u>)	51 (<u>44a</u>)	--
2	+ <u>43b</u>	--	70 ^c	15	100 (<u>45b</u>)	--	--
3	+ <u>43c</u>	--	70	15	82 (<u>45c</u>)	13 (<u>50</u>) ^a	5
4		Et ₃ N	70	68	90 (<u>45c</u>)	8 (<u>50</u>) ^a	2
5	+ <u>43d</u>	--	70	68	69 (<u>45d</u>)	--	31 ^b
6	+ <u>43f</u>	--	70	22	62 (<u>45f</u>)	--	38 ^b
7		Et ₃ N	70	98	94 (<u>45f</u>)	--	6
8	<u>46</u> + <u>43a</u>	--	41	98	95 (<u>48a</u>)	5 (<u>47a</u>)	--
9	+ <u>43b</u>	--	70 ^c	18	100 (<u>48b</u>)	--	--
10	+ <u>43c</u>	--	70	15	100 (<u>48c</u>)	--	--

TABLE 1 (Continued)

Run No.	Reactants	Catalyst	Temp.	% Conversion	% O-alkylation	% C-alkylation	% other
11		Et ₃ N	70	85	100 (<u>48c</u>)	--	--
12		--	100	42	100 (<u>48c</u>)	--	--
13	46 + <u>43d</u>	--	70	96	81 (<u>48d</u>)	--	--
					19 (<u>48a</u>)		
14	<u>43e</u>	--	70	87	100 (<u>48e</u>)	--	--
15	<u>43f</u>	--	70	31	100 (<u>48f</u>)	--	--

a- unstable

b- comprised of at least 4 compounds whose stability precluded further identification

c- sealed tube reaction

products all showed strong carbonyl absorptions (ir) but their nmr spectra were unintelligible in terms of simple alkylation products. They also decomposed rapidly on exposure to air and light. The esters 44d and 44f have been prepared by the action of α -haloesters on the potassium salt of 1,3-cyclohexanedione³⁵, but we were unable to isolate either of these from the reaction of the thallium salt. Of interest is that when the enol ether 48d was allowed to stand at room temperature and exposed to the atmosphere a clean conversion to 48a occurred over a period of some weeks. Although the enol ether 45a, 45c and 48c also decomposed under analogous conditions, many unidentified products were produced.

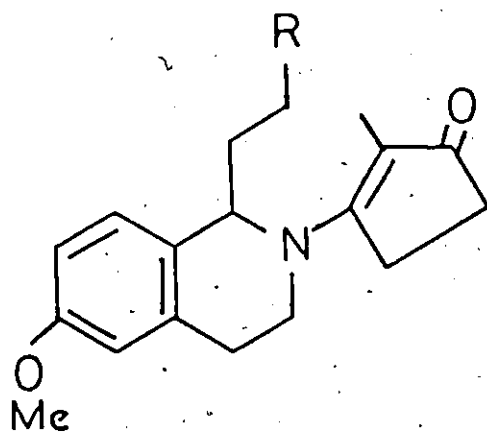
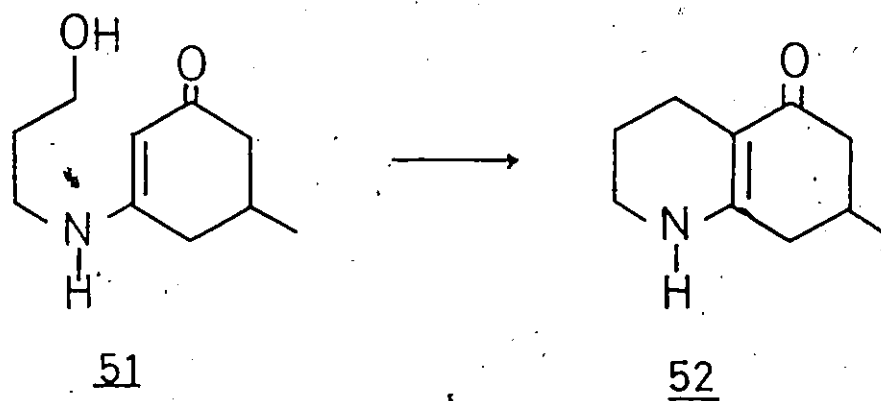
In general the data (Table 1) indicate a preference for C-alkylation in 42 relative to 46. As proposed previously³³ this result may be ascribed to the fact that O-alkylation of 42 forces the product to assume the half chair conformation whereas C-alkylation allows the product to exist in the more stable chair formation. In the case of 46, both the O- and C-alkylation products are relatively rigid and therefore stability gained by formation of the conjugated ketone takes precedence. Similar reasoning³⁶ has been used to rationalize the difference in the acidities of 1,3-cyclohexanedione and 1,3-cyclopentanedione. The remarkable stability of the enol in the cyclopentyl system

is exemplified by the fact that 2-methylcyclopentan-1,3-dione is not reduced by hydrogen over platinum catalyst³⁷.

Although there is no evidence as to the crystal structure of 42 and 46, it is felt that the results obtained can be attributed to steric prohibition of the proposed cyclic chelation and shielding of the C-2 carbon atom of the ambident nucleophile by the ring methylene groups. Another proposal (ref.24, p.523) has suggested that the regiospecificity in the acyclic cases may be due to the fact that the reactions are both heterogeneous and involve a cation which is tightly bound to oxygen, factors which are known to favor C-alkylation. Clearly the results obtained in this work do not support the postulate.

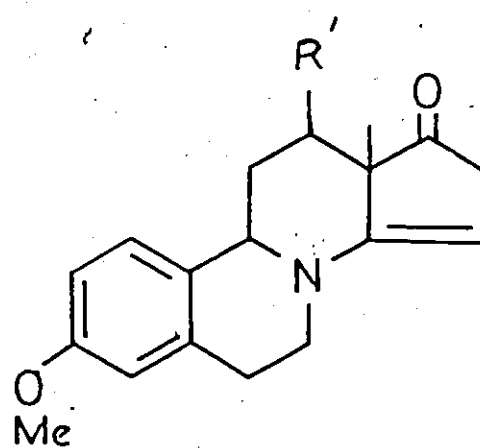
In summary, the results clearly indicate that the predilection of acyclic 1,3-diketones is not shared by their cyclic relatives. Recently these findings have been substantiated by a report³⁸ that exclusive C-alkylation in the acyclic salts takes place only with methyl iodide and is accompanied by dialkylated byproducts. Generally it seems that thallium salts of 1,3-diketones do not offer the special synthetic advantages for promoting exclusive mono-C-alkylation as originally claimed.

The failure of the thallium salts to produce C-alkylated products required us to approach our synthetic problem from a different perspective.



- a, R = OH
 b, R = Br
 c, R = COOEt

53



- a, R' = H
 b, R' = H
 c, R' = (=O)

54

FIG. 8. Enamine cyclizations

Enamine Cyclization

There are several examples in the literature of intramolecular cyclizations of enamines formed from 1,3-diketones (Fig.8). The cyclization of 51 to 52 was carried out with the use of pyridine hydroiodide³⁹. The yield of the reaction was not reported but has been quoted as "poor"^{40a}. Similarly, the formation of 54c by the cyclization of the ester 53c was not very successful^{40a}. This was attributed to the reluctance of the stable transoid keto-enamine to exchange its conjugated linkage for a less conjugated system present in the cyclized product. The unreactivity of ketoenamines is also exemplified by the inability to form the ketal of the carbonyl function in 53c^{40a}. The conversion of 53a to 54a was accomplished in high yield by heating in acetonitrile over a period of days. The bromide 53b was also cyclized in good yield with the use of silver perchlorate^{40b}.

These findings suggested a possible general route to the desired azabicyclooctane 25. The proposed synthetic scheme is outlined in Fig.9. The ketoenamine 56 was prepared in good yield by reacting the dione 35 with N-benzylethanolamine 55. The alcohol 56 was then heated with pyridine hydroiodide⁴¹ without solvent to 140°C. No reaction was observed and starting alcohol was recovered. The alcohol 56 was then heated for 7 days in acetonitrile and again no

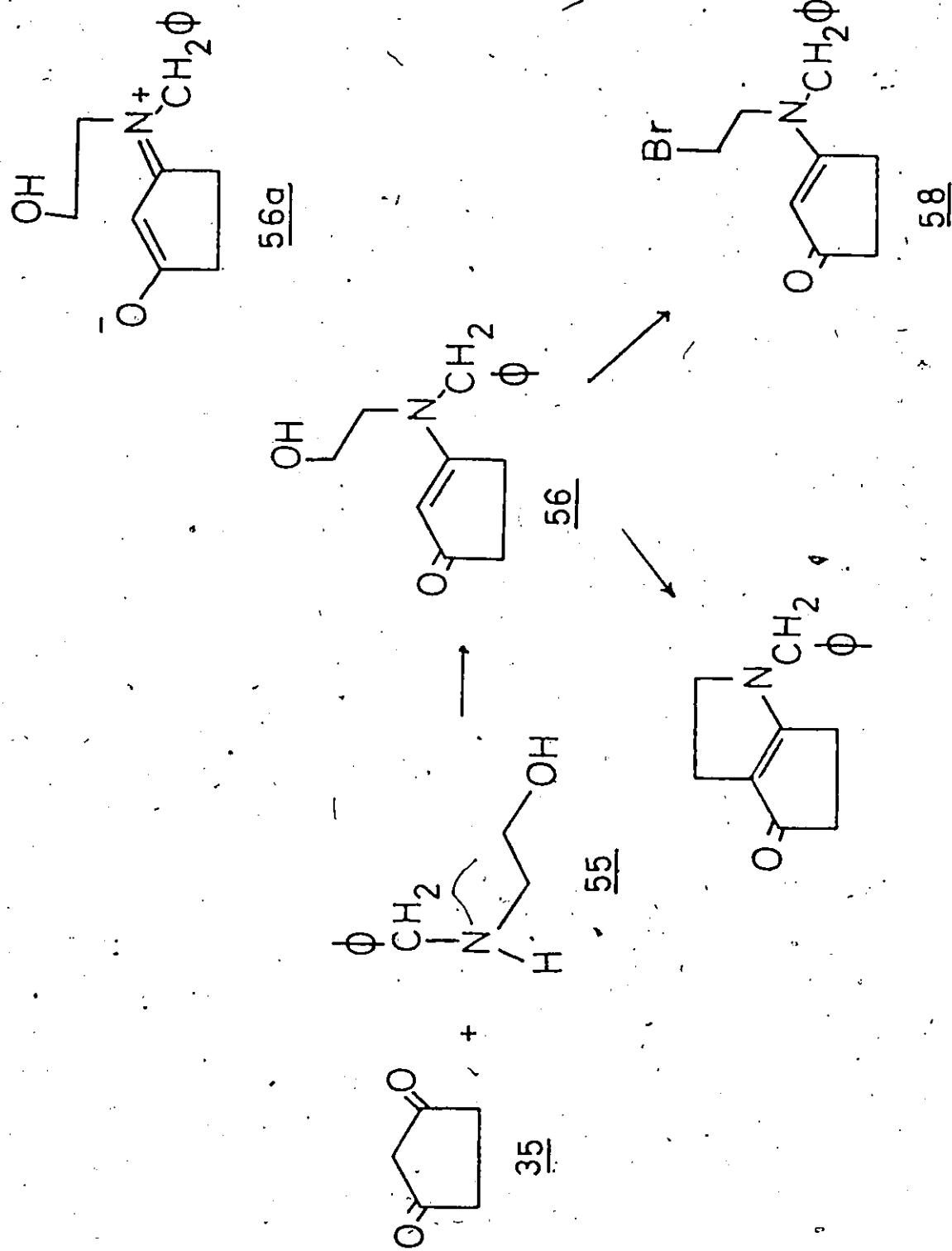


Fig. 9 Synthetic scheme via enamine cyclization

reaction took place. The bromide 58, prepared by the action of phosphorus tribromide on 56, was heated in refluxing dimethyl formamide with silver perchlorate for a period of 45 hours. A large amount of starting material was recovered as well as pure elemental silver, but no product could be isolated. These unsuccessful attempts to cyclize the ketoenamine 56 may be attributed to its unreactivity, as starting material was obtained in most cases. The ketoenamine 56 seems to be best represented as 56a as no carbonyl absorption is present in the infrared spectrum.

It was felt that the difficulties encountered with unreactive ketoenamines could be overcome with the use of aziridine enamines (Fig. 10). The electron-pair on the nitrogen atom in aziridine is not as available to contribute to the resonance structure 56a as in the acyclic amine case⁴². The cyclization of the ketoenamine 59 has been accomplished by heating in the presence of sodium iodide⁴³. Presumably, the sodium iodide opens the aziridine ring to form the intermediate 60 which cyclizes by displacement of iodide to give 61. The difference between this reaction, and the previously attempted cyclizations, is that no internal salt formation is possible which is thought to deactivate the molecule.

The diones 35 and 62 were converted to the vinylogous acyl bromides 63 and 65 in low yields with phosphorus tribromide. These bromides were converted to the enamines 64.

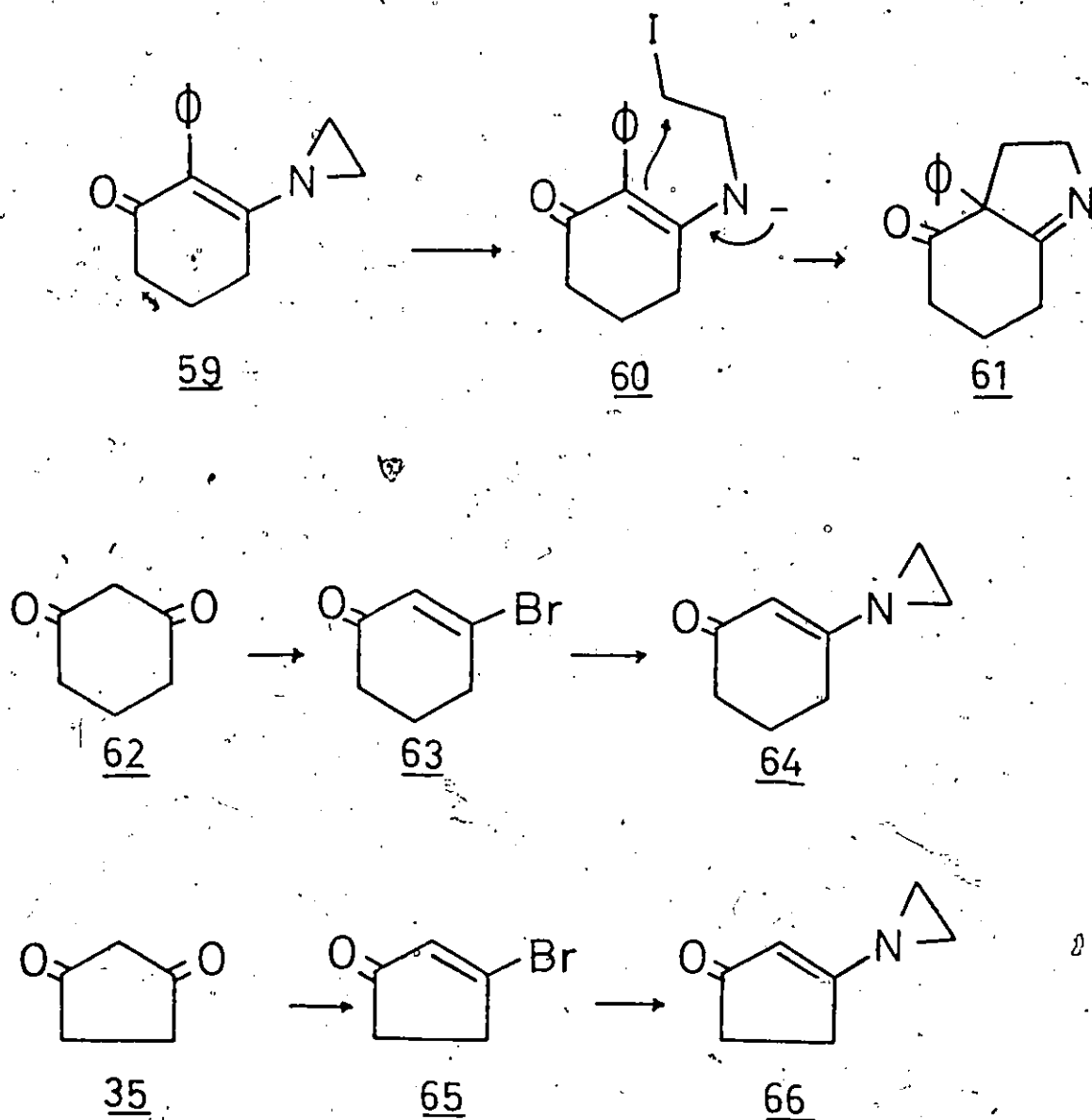


FIG. 10 Cyclization via aziridine enamines

and 66 by treatment with aziridine and triethylamine. When the enamine 66, which was unstable and polymerized when stored at -10°C , was heated with sodium iodide according to the reported procedure⁴³ it polymerized violently to a black tar from which no useful product could be isolated. Attempts to carry out the reaction in solvent were also unsuccessful.

The enamine 64 was found to be more stable, and was heated in several solvents in the presence of sodium iodide. In these reactions only starting material (64), and polymers were isolated. The instability of the enamines 64 and 66, low yields in the synthesis of precursors 63 and 65, and the inability to isolate any cyclized products led us to abandon this approach.

Vinyl triphenylphosphonium bromide Cyclization

In recent years there has been increasing interest in the use of vinyl triphenylphosphonium bromide (67) as a versatile reagent for the preparation of heterocyclic materials^{44a} (Fig. 11). The reaction involves initial formation of the heteroatom anion which adds in a Michael fashion to the salt 67. The phosphorane produced then undergoes a Wittig reaction with the carbonyl group, producing the cyclized product. The success obtained with this general technique led us to investigate its use for the synthesis of the bicyclic amine 25.

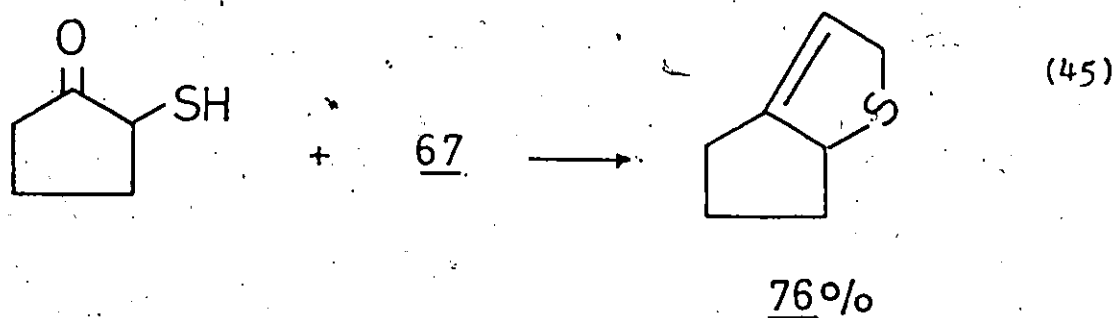
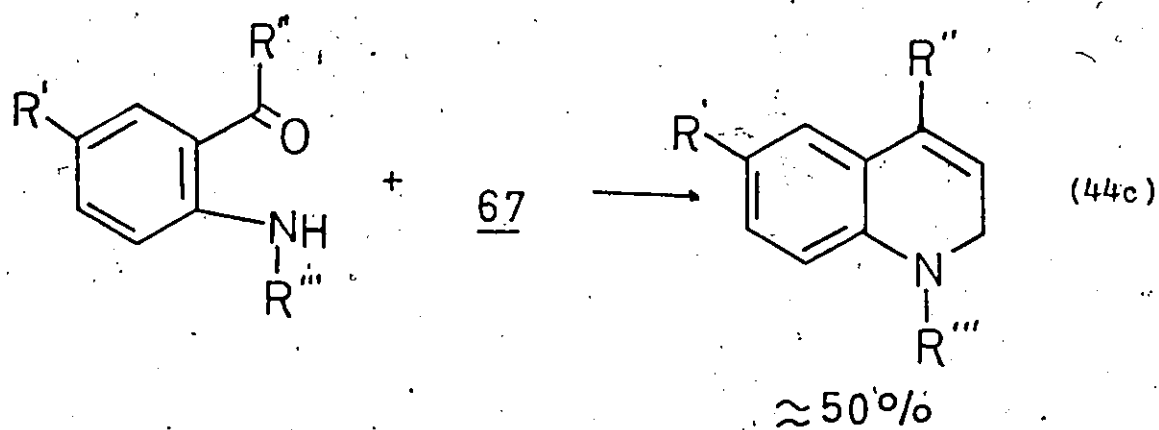
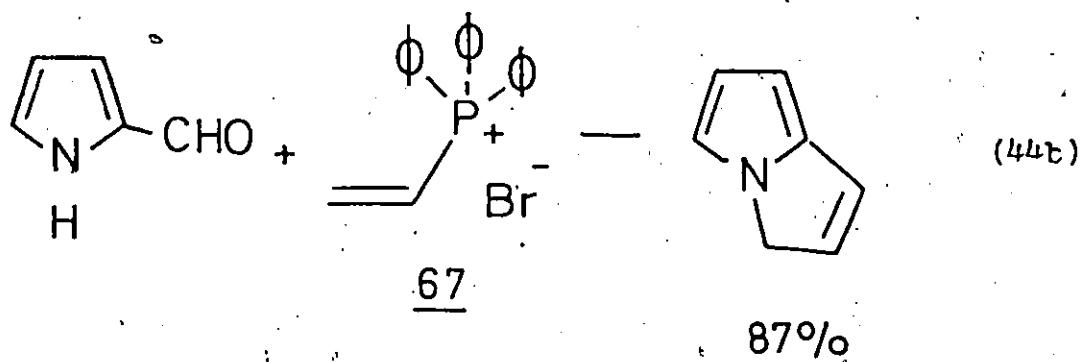


FIG. 11 Reactions of vinyl triphenylphosphonium bromide

The proposed synthetic scheme is outlined in Fig. 12. The reaction of the aminocyclopentanone 68 with 67 should

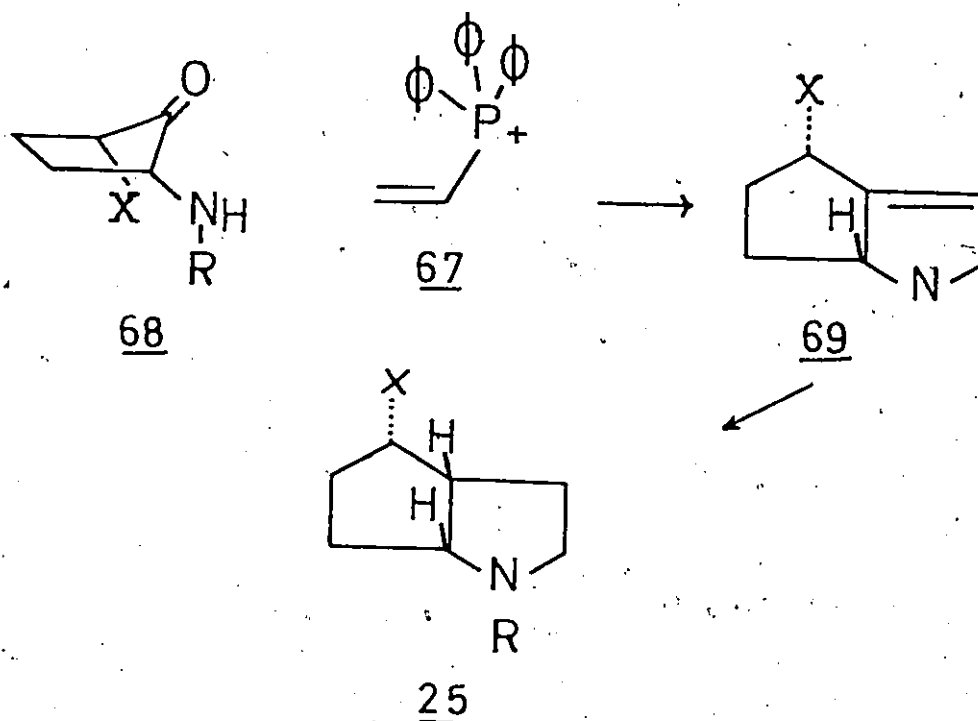


FIG. 12 Synthetic scheme using vinyl phosphonium salt

produce the cyclic olefin 69. Reduction of 69 would form 25 with the desired cis-ringfusion⁴³. If the functional group X is in a cis relationship with the amine group in 68, the end product 25 will have the cis-syn configuration desired for the fragmentation reaction. Therefore, our efforts were directed toward the preparation of 68 with the required cis relationship.

The synthetic scheme adopted for the synthesis is

outlined in Fig. 13. Bromination of 70 with pyridinehydrobromide perbromide according to the reported procedure⁴⁶ afforded 71, the yield of which was greatly improved if the reaction was carried out using bromine⁴⁷. Treatment of 71 with potassium t-butoxide gave the diene 72 which because of its reactivity, was never isolated but reacted in-situ with the dienophile. The diene failed to react with 1-chloro-1-nitrosocyclohexane (73)⁴⁸ even when the latter was present in large excess. Only the known dimer⁴⁶ of 72 and unreacted dienophile were isolated. Clearly, the nitroso compound 73 was a less reactive dienophile than 72.

The reaction was then carried out with the more reactive dienophile 75⁴⁹ and adduct 76 was obtained in moderate yield (Fig. 14). This adduct reduced with palladium on charcoal to 77. Previous workers⁴⁹ had attempted to generate the bridgehead ketone function in 77 using acid-catalyzed hydrolysis. It was found that 77 was stable to all conditions tried. Our interest was not in the generation of the ketone but in the formation of the hydrazo compound 78 as a source of the diamine 80⁵⁰. Although the generation of amines from amides proceeds best under acidic conditions, the stability of 77 to these conditions led us to attempt the conversion under basic conditions. The amide 77 was treated with refluxing aqueous KOH and KOH/ethylene glycol. Unfortunately, no useful products were isolated other than starting material (77).

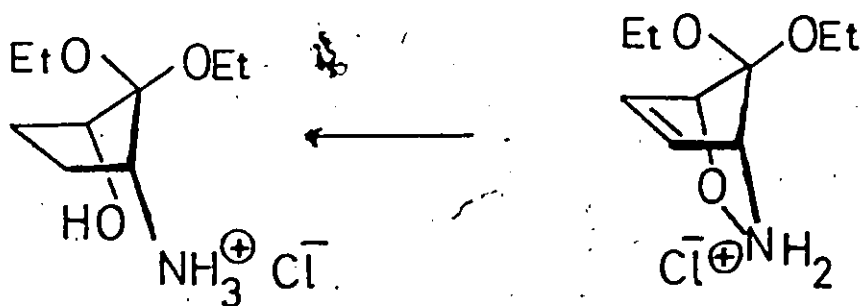
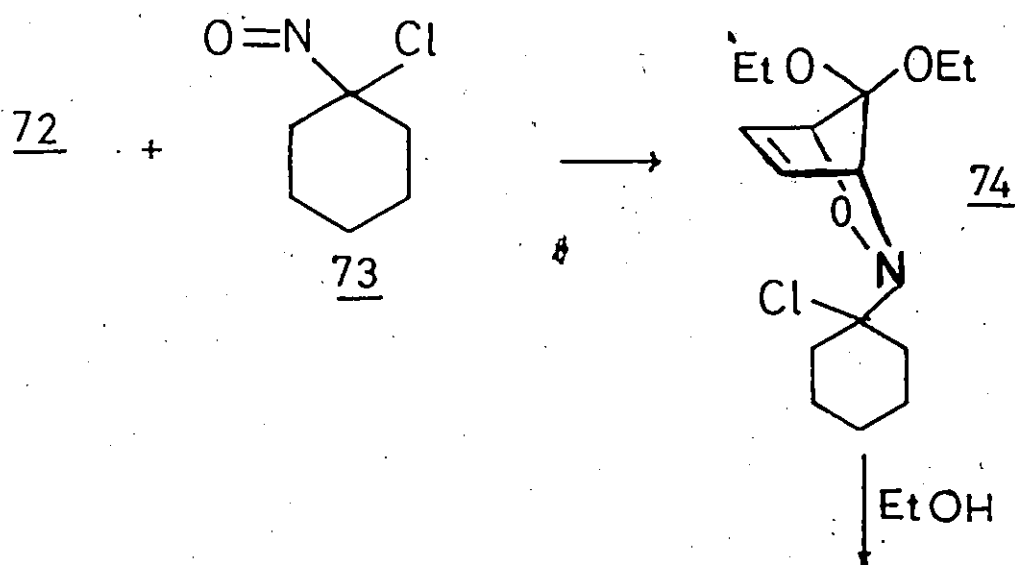
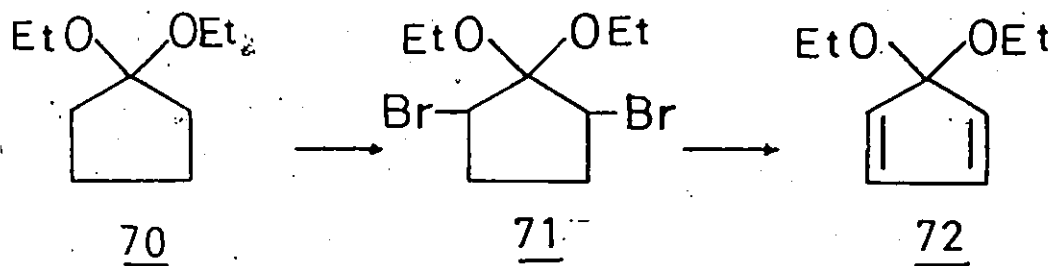
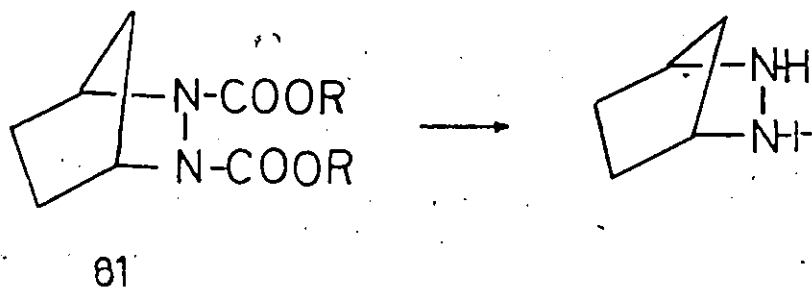


FIG. 13 Diels Alder reaction using 1-chloro-2-nitroso
cyclohexane

The reduction of amides with lithium aluminium hydride derivatives under controlled reaction conditions⁵¹ can be used to produce amines and aldehydes. Therefore, 27 was treated with sodium bis(2-methoxyethoxy) aluminium hydride (Vitrider) at 0°C. A mixture of products was isolated in which the main fraction was the dibenzylamine 29. Treatment of 27 with diisiamylborane in an attempt to obtain the required hydrazo 28, produced a mixture of five products, of which one seemed to be the required 28. Because of the low yield, this method was unacceptable. The dibenzylamine 29 was obtained in high yield by treating the amide 27 with lithium aluminium hydride. It appeared that hydrogenolysis of the benzylic amine 29 could afford the desired product. However, catalytic reduction over palladium catalyst failed to produce the product in good yield.

In the light of these results, a dienophile which could lead to a more easily hydrolyzed product was sought. The hydrolysis of the unsubstituted 81 had been reported by



several workers and did not present any difficulties⁵².

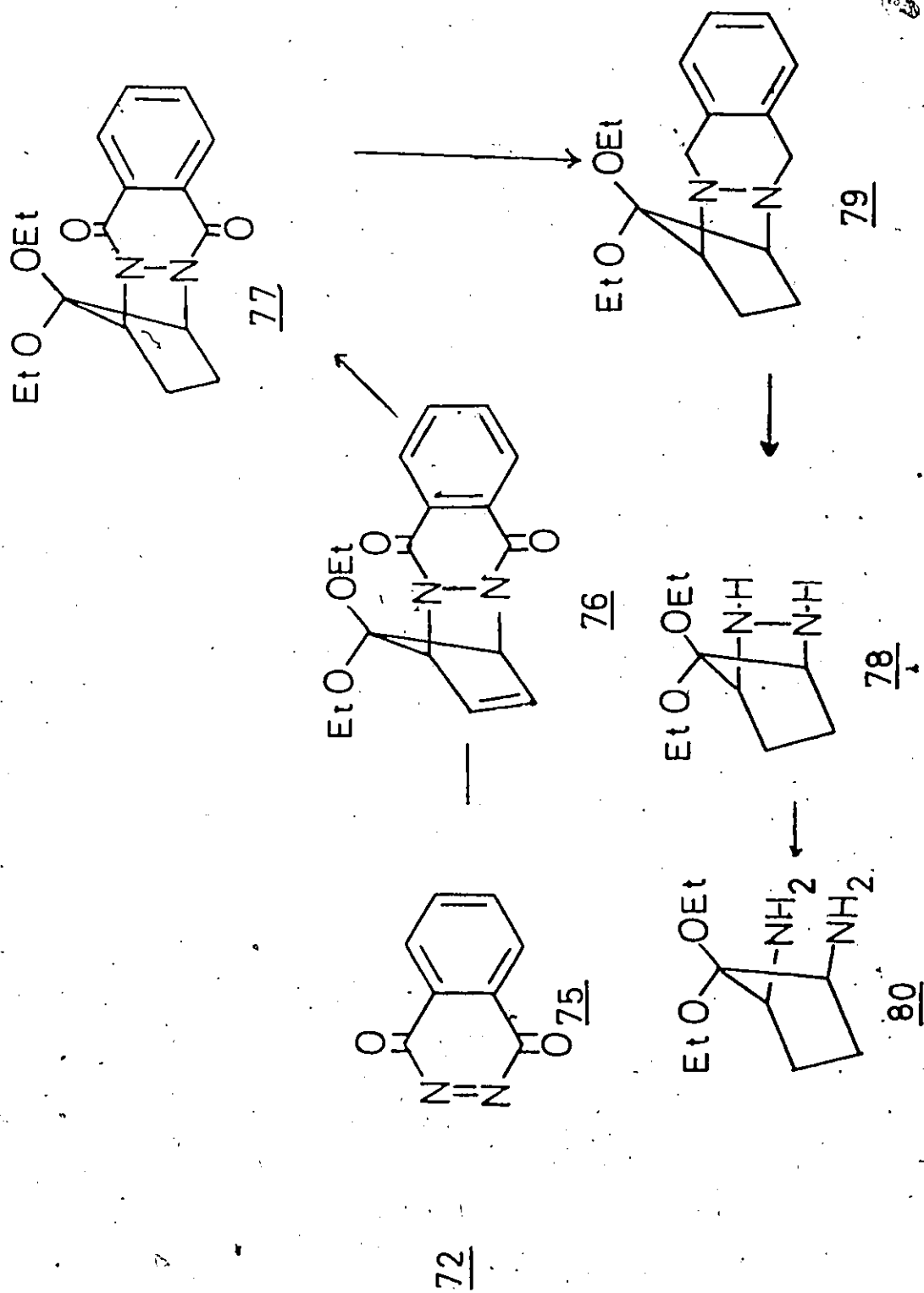
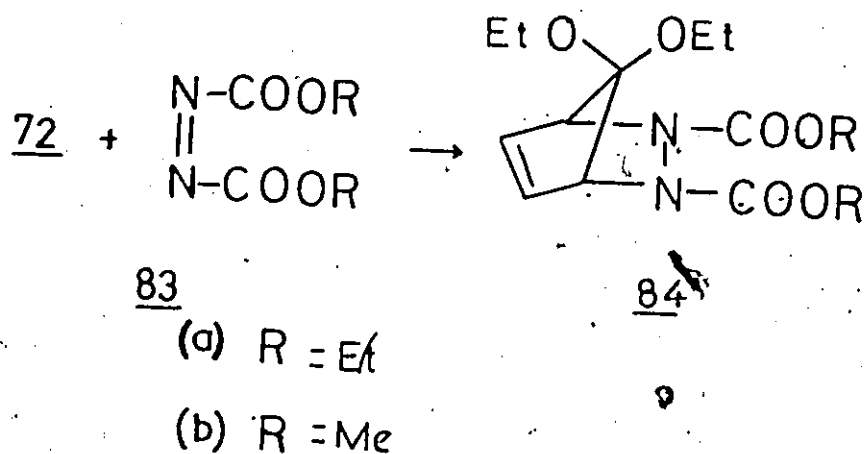
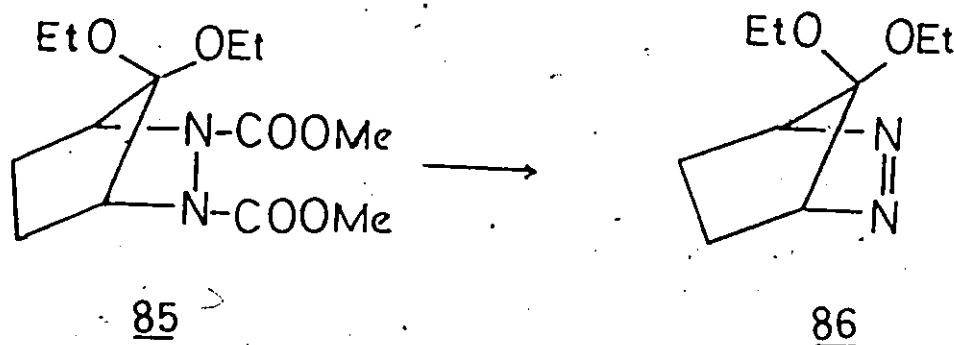


FIG. 14 Diels Alder reaction with 1,4-phthalazinedione 75

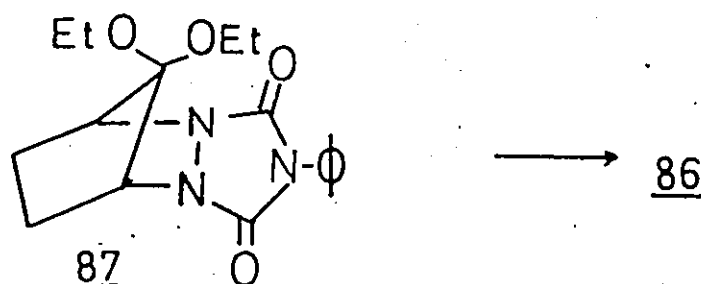


Utilization of ethyl diazodicarboxylate (83a) as a dienophile with 72 has been previously reported⁵³. The authors were unable to isolate the adduct 84a. We repeated this reaction and succeeded in isolating the adduct 84a, but the yield (15%) was unacceptably low. Replacing 83a with 83b increased the yield of the adduct to a point (40%) where it could be used in the synthesis. The reduction to 85 was effected with

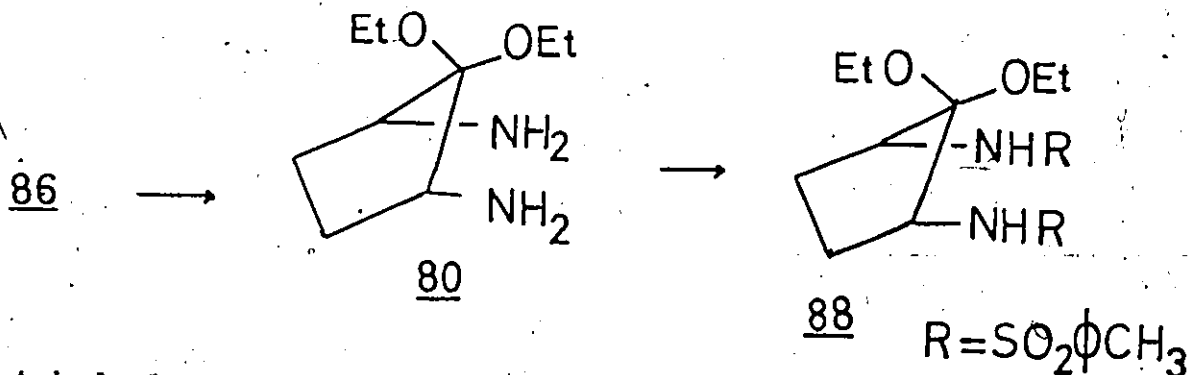


palladium on charcoal.

The hydrolysis of 85 was attempted according to the procedures established for the 7-unsubstituted system 81, but under these conditions, starting material was recovered. The hydrolysis was finally accomplished in low yield, but the product was oxidized to the azo compound 86 under the vigorous conditions. A similar reaction has been reported on the hydrolysis of 87. Reduction of 86 with palladium

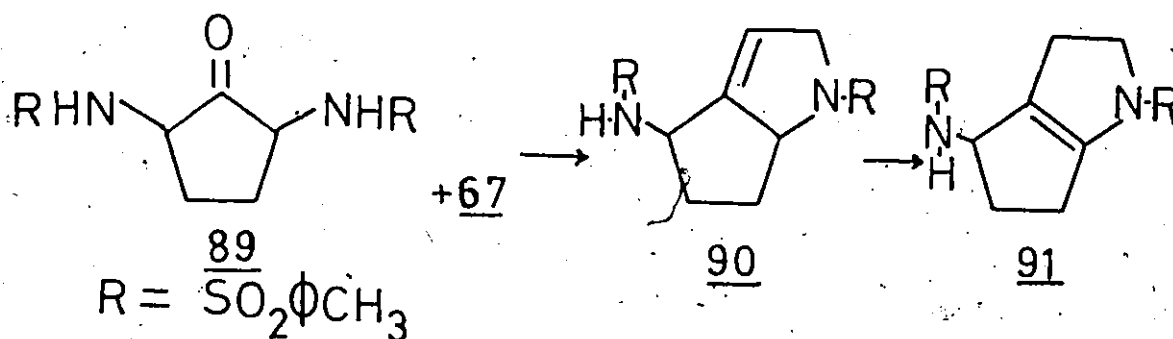


in 95% ethanol produced the diamine 80 directly. Acid hydrolysis of the ketal function was attempted but no reaction other than formation of the amine salt took place. The free amine 80 was then treated with *p*-toluenesulphonyl chloride and the disulphonamide 88 was formed which under-



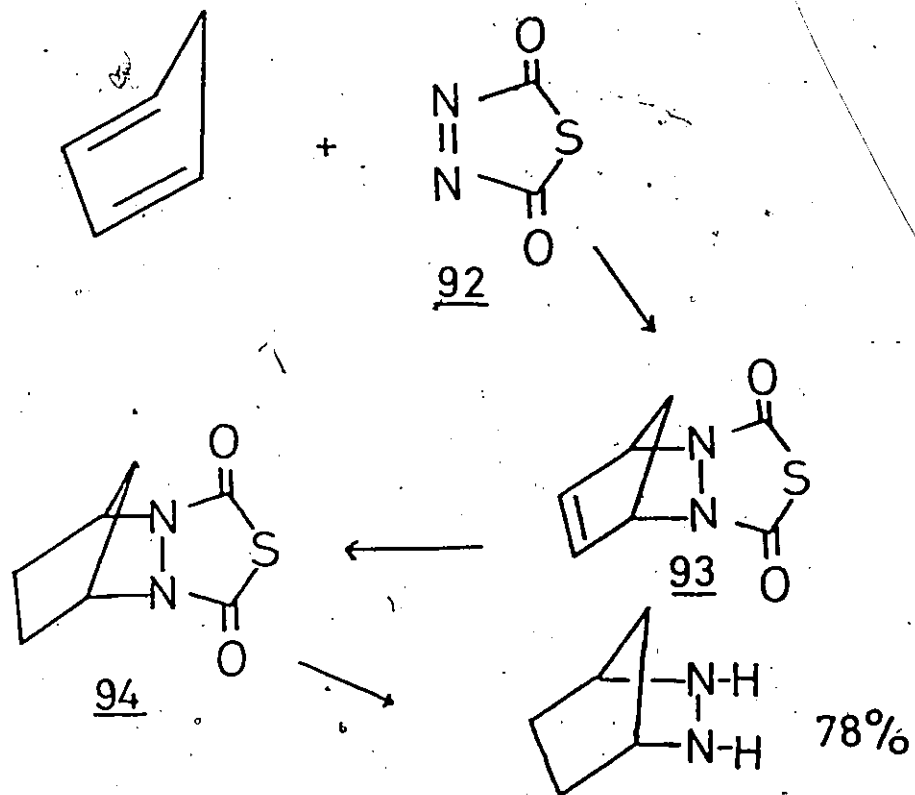
went hydrolysis to the ketone 89.

The cyclization of this material to the bicyclic compound 90 was attempted with vinyl triphenylphosphonium



bromide. The cyclization was successful, but the spectra (IR, nmr) indicated that the product obtained was 91. The project was stopped at this point because only a few milligrams of 91 were available.

The only serious problem encountered via this synthetic scheme was the hydrolysis of the Diels Alder adduct. The scheme could be greatly improved by using a dienophile which will form an easily hydrolyzed adduct. Since the completion of this work, such a dienophile, 1-thia,3,4-azo-2,5-dione (92) has been reported⁵⁵. This compound reacted with cyclopentadiene to produce the adduct 93 in 96% yield. The reduced adduct 94 was hydrolysed with .1N lithium hydroxide in water/diglyme at 25°C in high yield (78%). The application of this recent development would make the synthetic scheme much more practical.



There are several other approaches to the synthesis of 25 which were not investigated. These can be found in references 56 - 59.

EXPERIMENTAL

Unless otherwise noted infrared spectra were recorded on a Beckmann IR12 spectrometer in chloroform solution and nmr spectra were obtained in a JEOLCO C60HL spectrometer in deuteriochloroform and are reported in δ units relative to TMS. The glc analyses were carried out on F and M Models 720 and 5750 gas chromatographs utilizing a 8 ft. x 0.25 in. 20% SE-30 on Chromosorb W column. Preparative glc was performed using an 8 ft. x 0.375 in. column packed as above. Composition of mixtures was determined using a disc integrator. Microanalyses were performed by A.B. Gygli, Microanalysis Laboratory, Toronto, Ontario.

2-Formylpyrrole 27

The aldehyde 27 was prepared in 80% yield according to a reported procedure¹⁵; mp 42 - 43°C; IR: 3460, 3290, 3020, 1660cm⁻¹; nmr (CDCl₃), 6.2 - 6.3 (ring CH, m), 6.85 - 6.95 (ring CH, m), 7.05, 7.15 (ring CH, m), 9.4 (CH, s), 10.6 - 12.0 (NH).

Ethyl 2-(2-pyrrolyl) acrylate 29

To 77 g (0.23 mole) of the phosphorane 28⁶⁰ in 800 ml of benzene was added 20.9 g (0.22 mole) of 2-formylpyrrole (27). The mixture was refluxed for two hours, allowed to cool, and the solvent was distilled to yield 23.7 g (65.5%); b.p. 135 - 138°C, 2mm, m.p. 53 - 54°C; IR (CCl₄), 3340, 2880, 1700, 1690, 1630, 1370, 1270, 1220, 1175, 1125.

1100, 1040 cm^{-1} ; nmr (CCl_4), 1.15 - 1.4 (CH_2 , t, $J=6.8$ Hz),
3.95 - 4.35 (CH_3 , q, $J=6.7$ Hz), 5.9 - 6.15 (CH , d, $J=16.5$ Hz),
5.95 - 6.2 (ring CH, m), 6.25 - 6.45 (ring CH, m),
6.6 - 6.8 (ring CH, m), 7.3, 7.55 (CH , d, $J=16$ Hz),
9.85 (NH, s).

Injecting a pure sample of 29 in a gas chromatograph
(10 ft., $\frac{1}{8}$ in. o.d., 20% Se 30 at 165 $^{\circ}\text{C}$) isomerized 29 to
29a; IR. (CCl_4), 3270, 2990, 1690, 1610, 1601, 1220, 1190,
1130, 1085, 1090 cm^{-1} ; nmr (CCl_4), 1.4 (CH_2 , t, $J=8$ Hz),
4.26 (CH_3 , q, $J=8$ Hz), 5.4, 5.6 (CH , d, $J=12$ Hz), 6.17 -
6.30 (ring CH, m), 6.37 - 6.53 (ring CH, m), 6.6, 6.86
(CH , d, $J=12$ Hz), 6.86 - 7.1 (ring CH, m).

Heating 29 in triglyme at 200 $^{\circ}\text{C}$ for a period of 30 min.
did not produce any of the cis-isomer 29a. The latter was
also heated neat for 2 min. at 250 $^{\circ}\text{C}$ with no isomerization.

Ethyl 2-(2-pyrrole) propionate 30

To a solution of 3.3 g (.02 mole) of the ester 29
in 100 ml of absolute ethanol was added a catalytic amount
of palladium on charcoal. The mixture was placed under a
hydrogen atmosphere, and 1 eq. was taken up in 2 hours.
The mixture was then filtered and the ethanol removed
in vacuo, leaving 3.07 g (91%) of clear oil; IR: 3470,
3010, 1725, 1235, 1200, 1090, 1030 cm^{-1} ; nmr (CDCl_3),
1.25 (CH_2 , t), 2.2 - 3.0 (CH_2CH_2 , 2t), 4.15 (CH_3 , q),
5.8 - 6.0 (ring CH, m), 6.0 - 6.2 (ring CH, m), 6.58 - 6.7

(ring CH, m), 8.2 - 9.0 (NH, m).

2-(2-pyrrole) propionic acid 31

A mixture of 4 g (.024 mole) of the ester 30 and 6.5 ml of 7.5N potassium hydroxide was heated to 100° for 40 min. At the start of the heating period there were two layers, but after 40 min. the solution was homogeneous. The solution was then cooled and acidified with acetic acid (same preparation done, but dilute hydrochloric acid used to acidify the solution). No precipitate was observed, and solvent extractions (ether or chloroform) did not separate any of the desired product. The water was then evaporated in vacuo and the solid residue taken up in methanol. The insoluble material (KCl) was filtered off and the methanol evaporated in vacuo, leaving a brown solid (1 g); m.p. 245 - 247° C. IR: (KBr) - 3400, 2960, 1660, 1600, 1440 cm⁻¹; nmr, (CD₃OD), 1.9 (5H, s), 2.3 - 3.1 (4H, m), 5.8 - 6.1 (2H, m), 6.6 - 6.7 (1H, m).

The peak at 1.9 ppm could not be explained in terms of the desired product.

2-(2-pyrrole) acrylic acid 31a

A mixture of 1 g (.006 mole) of the ester 30 was heated to 100° C with 4 ml of 3.5N potassium hydroxide. After 30 min., the solution was cooled and acidified with acetic acid at which time a light brown solid precipitated from the solution. The latter was filtered off and dried:

collected; .6 g (72%) of solid: m.p. 175 - 177°C; IR: (KBr), 3360, 3200 - 2400, 1690, 1420, 1320, 1280, 1135, 1050, 975cm⁻¹; nmr (acetone-d₆), 6.07, 6.33 (CH, d, J=16Hz), 6.17 - 6.38 (ring CH, m), 6.50 - 6.70 (ring CH, m), 6.90 - 7.17 (ring CH, m), 7.47, 7.73 (CH, d, J=16 Hz) 9.25 (COOH, s), 10.34 - 11.46 (NH, m).

Several attempts to repeat this experiment on a larger scale failed to produce the required acid.

2-(2-pyrrole) propionic acid 31 from 31a

A mixture of .4 g (.003 mole) of the acid 31a in 20 ml of absolute ethanol was hydrogenated over palladium on charcoal. After 1 equivalent of hydrogen was taken up, the mixture was removed from the hydrogenation apparatus and filtered. The ethanol was evaporated in vacuo, and a light brown solid was obtained; 100% yield, m.p. 106 - 108°C, IR: (KBr), 3410, 3200 - 2600, 1710, 1695, 1440, 1325, 1240, 1120cm⁻¹; nmr (acetone d₆), 2.54 - 3.06 (CH₂CH₂, 2t), 5.8 - 6.12 (2 ring H, m), 6.66 (ring H, m), 8.12 (COOH, s).

2-acetylcyclopentane-1,3-dione²² 36

A mixture of succinic anhydride (100 g - 1mole) and anhydrous aluminium chloride (267 g - 2 mole) was suspended in 1000 ml of 1,2-dichloroethane. Isopropenyl acetate (100 g - 1 mole) was added over a period of 3 hours. After the addition was completed, the reaction mixture was stirred for 2 hours and then refluxed for 15 min. The cooled reaction mixture

was poured into 2500 ml of 1M hydrochloric acid and cooled to 0°C. The organic layer was separated, while the salt saturated water layer was extracted with chloroform. The combined organic extracts were dried over sodium sulphate and the solvent removed in vacuo. The residual oil was placed in a sublimator from which the product was isolated 22 g (17%), m.p. 65 - 67°C; IR (CHCl₃), 3015, 1710, 1640, 1590, 1445, 1410, 1370, 1340, 1240cm⁻¹; nmr (CDCl₃), 2.50 (CH₃, s), 2.33 - 3.0 (CH₂CH₂, m), 14.2 (H, s),
1,3-cyclopentanedione 35 from 36²²

A mixture of 1 g (.007 mole) of the trione 36 and 10 ml of .6M hydrochloric acid was refluxed for 40 min., allowed to cool and extracted with chloroform (3 x 25ml). The chloroform was evaporated and .76 g of solid were recovered. Spectra of this solid was identical in all respects with the starting material (36). Other attempts (15 - 20 hours) produced a mixture which did contain the desired ketone in 20% yield. NMR- (CDCl₃ + CD₃OD), 2.55 (CH₂CH₂, s), 6.05 (CH₂, s).

Catalytic Hydrogenation of 37

To a solution of 1 g (0.01 mole) of 4-cyclopentene-1, 3-dione¹⁵ (37) in 25 ml of 95% ethanol was added a catalytic amount of 5% palladium on charcoal, and the mixture was hydrogenated at room temperature and pressure. Continuous absorption of hydrogen occurred until 1.6 molar equivalents

was reached at which point the reaction stopped. The solution was filtered free of catalyst, the solvent was evaporated and the residue distilled (90° bath temperature, 0.5 mm). Analysis of the distillate (0.37 g) by plc (8' x 0.25" 20% SE-30, 125°) showed the presence of two compounds one of which had the same retention time as 2-cyclopentenone. No cyclopentanone was present. The spectra of the distillate identified the material as 3-hydroxycyclopentanone (40) from which the 2-cyclopentenone was formed by dehydration during g/c analysis; Ir 3610, 3450, 1737cm⁻¹; nmr 4.6(m, 1, CHOH), 3.58 (s, 1, -OH), 2.5 - 2.0 (m, 6). The residue from the distillation (0.6 g, 60%) was 1,3-cyclopentanedione (35), mp 151 - 152° (sublimed sample)(lit.²³ 149 - 150°).

Zinc Reduction of 37

To a mixture of 500 ml of glacial acetic acid and 100 g (1.54 mole) of activated zinc²⁷ in a 2 l. flask equipped with a mechanical stirrer and maintained at 95° with an oil bath was added a solution of 20 g (0.21 mole) of 37 in 300ml of glacial acetic acid over a period of 2 hours. The mixture was stirred at 95° for 1 hr, filtered, cooled to room temp. and filtered again. Evaporation of the solvent at reduced pressure afforded a light yellow residue which gave 35 (15.5 g, 76%) on recrystallization from methanol-ethyl acetate (1:3) at -78°; m.p. 148 - 149°. Anal. Calcd. for C₅H₆O₂: C, 61.22; H, 6.16. Found: C, 61.25, H, 6.13.

Preparation of Salts 42 and 46

1,3-Cyclohexanedione or 1,3-cyclopentanedione (35) was dissolved in a mixture of benzene and ethanol (2:1) and thallium ethoxide (61) was added dropwise with stirring. The salt precipitated from solution, was collected by filtration and recrystallized from ethanol. The yields were quantitative.

1,3-cyclohexanedione thallium salt 42; m.p. 191 - 192°;
IR(KBr): 3410, 2940, 1655, 1540, 1415, 1375, 1320.

1,3-Cyclopentanedione thallium salt 46; mp 205 - 206°;
Ir(KBr): 3380, 2920, 1635, 1560, 1360, 1280.

General Alkylation Procedure

The thallium (I) salt (42 or 46) was suspended in 15 ml of the alkylating agent and heated at constant temperature. The cooled reaction mixture was filtered and the residue was washed with 30 ml of benzene. The combined filtrates (Fraction A) were evaporated to afford crude material which was immediately subjected to glc analysis. Preparative glc afforded samples of each of the components for spectral and elemental analysis. The residue from the filtration was then washed with absolute methanol to remove the thallium halide; the filtrate (Fraction B) was evaporated and the crude material was analyzed. In each case, most of the unreacted 42 or 46 was recovered from this fraction. Only other products are mentioned below. The relative amounts

of products are shown in Table 1 and the spectral data are summarized in Tables 2 and 3. Catalysis was accomplished by adding three drops of triethylamine to the reaction mixture.

Methyl Iodide and 42

Fraction A (0.5 g) containing 41% of 49⁶² and 59% of 45a³⁵ which were identical in all respects with authentic samples was obtained from 3.1 g of 42 (9.8 mmole). Fraction B afforded 0.7 g of 44a mp 198 - 200° (lit.³⁴ 204°).

Methyl Iodide and 46

Fraction A (0.7 g) identical in all respects with 48a²⁶ was obtained from 2.0 g (6.78 mmole) of 46. Fraction B gave 0.3 g of 47a mp 207 - 208°C (lit.⁶⁴ 208 - 209°).

Ethyl Bromide and 42

Fraction A (0.1 g) was obtained from 1.5 g (4.92 mmole) of 42 and consisted entirely of 45b identical with an authentic sample³⁵.

Ethyl Bromide and 46

Fraction A (0.1 g) identified as 48b was obtained from 1.3 g (4.45 mmole) of 46 in the usual manner.

Anal. Calcd for $C_7H_{10}O_2$: C, 66.65; H, 7.99. Found: C, 66.61; H, 8.22.

Fraction B afforded 46 as the only isolable material.

1,2-Dibromoethane and 42

Fraction A (0.4 g) was obtained from 3 g (9.85 mmole)

of 42. From this material 45c could be isolated by glc.

Anal. Calcd for $C_8H_{11}BrO_2$: C, 43.57; H, 5.04; Br, 36.47.

Found: C, 43.86; H, 5.06; Br, 35.84.

Two other compounds were present, one of which presented spectral data consistent with 50. Mass spectral analysis gave a molecular weight of 138 ($P+1=9\%$, $P+2=1\%$). $C_8H_{10}O_2$ requires $P+1 = 8.9\%$, $P+2 = 0.7\%$ ⁶⁵. Other prominent peaks in the mass spectrum occurred at m/e 111, 110 (base), 80, 68. The instability of the compound prevented our obtaining a satisfactory elemental analysis.

Again, Fraction B afforded 42 as the only product.

1,2-Dibromoethane and 46

Fraction A (0.2 g) identified as 48c was obtained from 2.0 g (6.78 mmole) of 46.

Anal. Calcd for $C_7H_9BrO_2$: C, 40.98; H, 4.39. Found: C, 41.02; H, 4.34.

Fraction E afforded 46 as the only isolated material. Increasing the temperature to 100° raised the yield of 48c to 42% while adding three drops of triethylamine to the reaction afforded 48c in 85% yield.

Methyl bromoacetate and 42

Fraction A (0.96 g) was obtained from 2.4 g (7.72 mmole) of 42. From this material could be isolated 69% of 45d.

Anal. Calcd. for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.49; H, 6.75. The remainder of this fraction was comprised of four

TABLE 2
NMR Spectra of the Alkylation Products a,b

Compound	No.	
44a ^c	2.50 (t, 4, J=6, ring), 2.15 (s, 3, $\underline{\text{CH}_3}$), 1.88 (q, 2, J=6, ring).	
45a	5.40 (s, 1, -C=CH-), 3.76 (s, 3, -OCH ₃), 2.57 - 1.75 (m, 6, ring).	
49	2.75 (t, 4, J=6 ring), 2.05 (q, 2, J=6 ring), 1.36 (s, 6, CH ₃ -C-CH ₃).	
45b	5.20 (s, 1, C=CH), 3.55 (q, 2, J=7, OCH ₂ CH ₃), 2.60 - 1.72 (m, 6, ring).	
	1.36 (t, 3, J=7, CH ₂ CH ₃).	
50	4.52 (t, 2, J=10, CH ₂ -CH ₂ -O), 3.00 - 1.82 (m, 8).	
45c	5.37 (2, 1, C=CH-), 4.20 (t, 2, J=6, -OCH ₂ CH ₂ -), 3.61 (t, 2, J=6, O-CH ₂ CH ₂ Br), 2.65 - 1.8 (m, 6, ring).	
45d	5.11 (s, 1, -C=CH-), 4.47 (s, 2, -O-CH ₂ -COOR), 3.78 (s, 3, -COOCH ₃), 2.7 - 1.7 (m, 6, ring).	
45f	5.17 (s, 1, -C=CH-), 4.45 (s, 2, -O-CH ₂ COOR), 4.20 (q, 2, -CO ₂ CH ₂ CH ₃), 2.7 - 1.7 (m, 6, ring), 1.30 (t, 3, J=7, CO ₂ CH ₂ CH ₃).	

TABLE 2 (Continued)

Compound	No.
47a ^c	9.56 (s, 1, OH), 2.60 (m, 4, ring), 2.00 (s, 3, CH ₃).
48a	5.45 (s, 1, -C=CH), 3.97 (s, 3, -OCH ₃), 2.82 - 2.40 (m, 4, ring).
48b	5.23 (s, 1, C=CH-), 4.02 (q, 2, J=6.5, OCH ₂ -CH ₃), 2.73 (m, 4, ring), 1.38 (t, 3, J=7.5, CH ₂ -CH ₃).
48c	5.23 (s, 1, C=CH), 4.33 (t, 2, J=5.3, -O-CH ₂ -CH ₂), 3.59 (t, 2, J=5.3, CH ₂ CH ₂ -Br), 2.75 - 2.3 (m, 4, ring).
48d	5.20 (s, 1, C=CH), 4.57 (s, 2, O-CH ₂ -COOR), 3.80 (s, 3, COOCH ₃), 2.8 - 2.3 ⁶ (m, 4, ring).
48e ^d	5.15 (s, 1, C=CH), 4.60 (s, 2, -O-CH ₂ -COOR), 4.26 (q, 2, J=7.5, CO ₂ -CH ₂ -CH ₃), 2.80 - 2.25 (m, 4, ring), 1.25 (t, 3, J=7.5, CO ₂ CH ₂ CH ₃).

(a) Tabulation follows the order chemical shift (value), multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet), number of protons, coupling constant, and assignment of protons.

(b) In deuteriochloroform unless otherwise noted.

(c) In pyridine - d₆

(d) In carbon tetrachloride

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TABLE 3
Infrared Spectra of the Alkylation Products (cm⁻¹)^a

Compound No.

<u>44a</u> ^c	3100, 1580
<u>45a</u>	1670, 1645, 1610
<u>49</u>	1730, 1700, 1464
<u>45b</u> ^b	1680, 1660(sh), 1610
<u>50</u>	1630(vs)
<u>45c</u> ^b	1650, 1600
<u>45d</u>	1768, 1750(sh), 1670, 1620
<u>45f</u>	1761, 1740(sh)
<u>48b</u>	1705, 1680, 1600
<u>48c</u>	1710, 1687, 1592
<u>48d</u>	1765, 1705, 1685, 1605
<u>48e</u> ^b	1765, 1740, 1710, 1608

(a) In chloroform solution unless otherwise specified

(b) In carbon tetrachloride solution

(c) As potassium bromide dispersion

compounds in approximately equal amounts whose spectral characteristics indicated that they were not products of simple alkylation of 42 and which rapidly decomposed on standing.

Methyl bromoacetate and 45

Fraction A (1.7 g) which consisted of 18% 48a and 77% of 48d was obtained from 2.0 g (6.78 mmole) of 45.

Anal. Calcd for $C_8H_{10}O_4$: C, 56.47; H, 5.92. Found: C, 56.44; H, 5.89.

That 48a was a product of decomposition of 48d was shown by analysis of a sample of 48d which had been allowed to stand at room temperature for a period of several days. It had been cleanly converted to 48a. No rearrangement took place when air was excluded.

Fraction B consisted entirely of unreacted 46.

Ethyl bromoacetate and 46

Fraction A (1.6 g) was obtained from 2.8 g (9.36 mmole) of 46. The major (93%) component was identified as 48e. The remainder of the fraction was composed of several small impurities which were not investigated.

Anal. Calcd. for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.77; H, 6.69.

Again, Fraction F was entirely unreacted 46.

Ethyl chloroacetate and 42

Fraction A (0.47 g) was obtained from 3 g (9.85 mmole) of 42. From this material 45f was isolated.

Anal. Calcd. for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found:
C, 58.77; H, 6.69.

The remainder of the product was comprised of at least four compounds whose IR and nmr spectra were not consistent with products of simple alkylation and which rapidly decomposed.

Fraction B afforded only unreacted 42.

Ethyl chloroacetate and 46

Fraction A (0.25 g) was obtained from 1.3 g (4.35 mmole) of 46 in the usual manner. This material consisted entirely of the O-alkylated product 48e (=46f). Unreacted 46 was the only compound in Fraction B.

N-benzyl-N-(2-hydroxyethyl)-3-aminocyclopentenone 56

To 2.63 g (0.03 mole) of the dione 35 in 200 ml of benzene, was added 4.05 g (0.03 mole) of N-benzylethanolamine (55). The mixture was refluxed for 3 hours with continuous water removal. The benzene was then removed in vacuo, leaving a thick yellow oil, 3.5 g (57%); IR: 3300, 2020, 1660, 1590, 1570, 1450cm^{-1} ; nmr (CDCl_3), 2.15 - 2.50 (2H, d, $J=5$), 2.45 - 3.00 (2H, m), 3.20 - 3.60 (2H, m), 3.50 - 4.0 (2H, m), 4.35 - 4.7 (4H, d, $J=7.5$), 4.9 - 5.1 (1H, d, $J=7.5$), 5.6 (1H, s), 6.9 - 7.3 (5H, m); nmr - (CDCl_3), 1 drop D-trifluoroacetic acid - 2.6 - 3.2 (4H, m), 3.5 - 4.0 (4H, m), 4.6 - 4.8 (2H, d), 6.9 - 7.4 (5H, m).

Reaction of 56 with Phosphorus tribromide

To 1.5 g (.007 mole) of the alcohol 56 dissolved in

75 ml of chloroform at 0°C was added 10 g (.036 mole) of PBr_3 in 25 ml of chloroform. The reaction mixture was stirred for 20 hours at 0°C after which time it was heated to 45-50°C for 2 hours. The reaction mixture was then allowed to cool to room temperature and poured into 20 ml of ice water. The chloroform layer was separated and combined with the chloroform washings (5 x 100ml) of the water layer.

The chloroform was removed in vacuo and a .95 g (45%) dark redish oil remained; IR: 3010, 1660, 1565, 1430, 1220 cm^{-1} ; nmr (CDCl_3), 2.3 - 2.6 (2H, m), 2.65 - 2.95 (2H, m), 3.35 - 3.90 (4H, m), 4.6 (2H, s), 5.15 (1H, s), 7.0 - 7.45 (5H, m).

Reaction of 57 with silver perchlorate

A mixture of .7 g (.0026 mole) of the bromide and 1 g (.005 mole) of silver perchlorate in 25 ml of dimethylformamide was refluxed for 45 hours. The solution from which had precipitated elemental silver, was then cooled to room temperature and added to 100 ml of water which was then made basic with sodium hydroxide. The water layer was then extracted with four 100 ml portions of chloroform. The chloroform extracts were combined, washed with 50 ml of water, and then dried over anhydrous potassium carbonate. The drying agent was then filtered off and the chloroform removed in vacuo, leaving a dark liquid (.3 g). Analysis of this liquid (V.P.C. 10', $\frac{1}{8}$ " OD, 10% SE30) showed three

components of which one was 77% of the mixture. This component was collected from the chromatographic column ; IR: 1750, 1670, 1435, 930cm^{-1} ; nmr (CDCl_3), 2.20 - 2.25 (3H, d), 2.25 - 2.5 (2H, m), 3.1 - 3.5 (3H, m), 4.0 - 4.5 (4H, m), 7.0 - 7.25 (5H, d). This data does not fit the spectra of the expected cyclized product. No cyclized product could be isolated.

Reaction of alcohol 56 with pyridinium iodide

Pyridinium iodide was prepared by adding pyridine to a benzene hydrogen iodide solution. The solid isolated gave the correct melting point.

A mixture of 1.3 g (.006 mole) of the alcohol 56 and 1.5 g (.007 mole) of pyridinium iodide was heated without solvent for 3 hours. The mixture was then poured into ice water.. basicified with sodium hydroxide and extracted with chloroform (3 x5ml portions). The chloroform extracts were dried over potassium carbonate and then the chloroform was evaporated. The oil which remained gave identical spectra as the starting alcohol 56.

Reaction of alcohol 56 and acetonitrile

A sample (1 g) of the alcohol 56 was heated in 16 ml of acetonitrile for 8 days. After this time the acetonitrile was evaporated in vacuo and spectra obtained on the remaining alcohol. The spectra was identical in all respects to the starting alcohol 56.

3-bromocyclopentenone, 65

To 10 g (.1 mole) of the dione 35, in 300 ml of chloroform, was added 10 g (.037 mole) phosphorus tribromide. The reaction mixture was allowed to stir at room temperature for 24 hours. The solvent was removed in vacuo and the residue was added to 100 ml of ice water. The water mixture was then extracted with 4 x 50 ml portions of chloroform. The combined chloroform extracts were dried over sodium sulphate, filtered, and the solvent evaporated leaving an oil which crystallized in the refrigerator. Recovered 7 g of crude product (35%); IR: 3020, 1715, 1590, 1260, 1060, 990, 980 cm^{-1} ; nmr (CDCl_3), 2.4 - 2.65 (CH_2CO , m), 2.8 - 3.1 (CH_2CBr , m), 6.3 - 6.4 (CH , m).

3-bromocyclohexenone 63

This bromide was prepared in a similar manner as the cyclopentyl system. The product was obtained in 72% yield. IR: 1680, 1615, 1330, 1290, 980 cm^{-1} ; nmr; 1.8 - 2.5 ($\text{CH}_2\text{CH}_2\text{CO}$, m), 2.6 - 2.9 (CH_2CBr , t), 6.36 (CH , m).

Anal. Calcd for $\text{C}_6\text{H}_7\text{BrO}$: C, 41.41; H, 4.06; Br, 45.91.

Found: C, 41.33; H, 4.29; Br, 45.43.

N-(3-oxocyclopentenyl) aziridine 66

The aziridine used to make the enamine was prepared from ethanolamine in 83% yield according to the procedure of W. Reeves⁶⁶. A mixture of 3.5 g (.022 mole) of the bromide 65, and 6.5 g (.15 mole) of aziridine and 6.5 g (.059 mole)

of triethylamine in 100 ml anhydrous ether was allowed to stir at room temperature under nitrogen for 8 days. The triethylamine hydrobromide was filtered off and the volatiles evaporated in vacuo leaving 1.3 g (50%) of oil. IR: 3380, 3020, 2940, 1710, 1690, 1600, 1375, 1300, 1190, 1160 cm^{-1} ; nmr. (CDCl_3), 2.15 ($\text{CH}_2\text{CH}_2\text{N}$, s), 2.2 - 2.7 (CH_2CH_2 , m), 5.35 (CH, m).

N-(3-oxocyclohexenyl) aziridine 64

This cyclohexylenamine was prepared in the same manner as the cyclopentylenamine in 72% yield; IR: 3300, 3000, 1650, 1600, 1390, 1340, 1250, 1160, 1140 cm^{-1} ; nmr, 2.1 ($\text{CH}_2\text{CH}_2\text{N}$, s), 2.2 - 2.6 (CH_2CH_2 , m), 5.48 (CH, s).

Reaction of 66 with sodium iodide

On heating 1 g of 66 with 2 g of sodium iodide according to the procedure outlined by H. Whitlock⁴³ a violent polymerization took place. No product of any kind could be isolated from the charred polymer.

The enamine 66 was heated to 50°C in tetrahydrofuran in the presence of sodium iodide for 24 hours. All that was isolated from this reaction was a pale yellow rubbery polymer.

Reaction of 64 with sodium iodide

A mixture of 1 g (.007 mole) of 66, in 100 ml of ether with a catalytic amount of sodium iodide was stirred for 6 days after which time the solution was filtered and

the solvent evaporated in vacuo. The precipitate which was obtained was insoluble in alcohol, chloroform, water and had a rubber texture. The liquid isolated was starting material.

2,5-dibromocyclopentanone diethylketal ^{46b} 71

Pyridinium bromide perbromide ⁶⁷ (83.0 g - .228 mole) was added to cyclopentanone diethylketal (70) (18.0 g - .114 mole) in 225 ml of dry ethanol at 6 - 10°C. The mixture was stirred magnetically. Over the course of an hour, the red color of bromine was discharged. Towards the end of the reaction the ice bath was removed and the solution was allowed to come to room temperature. The reaction mixture was then added with stirring, to 250 ml of 10% aqueous sodium bicarbonate. The oil which separated out was taken up in pentane while the aqueous phase was extracted several times (5 x 100 ml) with pentane. The combined pentane extracts were washed alternately with a 3% sodium bicarbonate solution and 3% hydrochloric acid solution. After the last washing with base, the extracts were washed with saturated brine solution and dried over sodium sulphate. The pentane solution was then rapidly passed through a small column of neutral alumina. Evaporation of the solvent in vacuo gave a colourless oil, 27 g (75%); nmr (CDCl₃), 1.05 - 1.45 (2CH₃, m), 2.0 - 2.8 (CH₂CH₂, m), 3.4 - 4.0 (2CH₂, m), 4.10 - 4.55 (CHBr, m).

The bromide 71 was also prepared in higher yield using bromine⁴⁷.

Cyclopentadiene ethyl ketal 72⁴⁶

The crude dibromoketal 71 (12.3 g - .04 mole) in 25 ml of dimethyl sulfoxide (previously dried over molecular sieves) was added dropwise to a well stirred solution of 17 g (.15 mole) of potassium t-butoxide in 100 ml of dry dimethyl sulfoxide at 18 - 20°C. The addition was carried out as quickly as possible keeping the temperature below 20°C. All the following steps were carried out as quickly as possible. After the addition was completed the reaction mixture was added with stirring to iced water. The black mixture was extracted with cold pentane several times (5 x 100 ml). The combined extracts were washed several times with small amounts of ice water, then with saturated brine. The solution was dried over sodium sulphate. The pentane solution was kept at -78°C to prevent dimerization of the diene. The presence of the latter was ascertained by forming the Diels Alder adduct with maleic anhydride⁴⁶:
nmr (CDCl₃), 1.0 - 1.35 (2CH₃, 2t), 3.2 - 3.55 (2CH₂, m), 5.5 - 5.7 (2CH, m), 6.1 - 6.25 (=CH, t, J=1.5 H₂).

1-chloro-1,nitrosocyclohexane 73

The nitroso 73 was prepared from the oxime precursor according to a reported procedure⁴⁸ in 89% yield; IR: 2950, 2865, 1705, 1580, 1450cm⁻¹; nmr (CDCl₃), 1.45 - 3.0

(CH₂, m).

Reaction between diene 72 and 73

The diene was generated according to the described procedure. To a calculated 5.7 g (.034 mole) of the diene 72 in 200 ml of pentane was added 6 g (.039 mole) of the nitroso 73 and 10 ml of ethanol. The reaction was kept at -10°C overnight. Since no apparent discoloration had occurred, another 6 g of the dienophile 73 was added. After an additional 5 hours the nitroso 73 was distilled off leaving a residue; nmr (CDCl₃), 1.0 - 1.4 (4CH₃, m), 2.8 - 3.1 (3H, m), 3.2 - 3.4 (10H, m), 4.45 - 4.60 (1H, m), 5.80 - 6.10 (3H, m).

The nmr is identical with a dimerized sample of 72.

Reaction of 1,4-phthalazinedione 75 with 72

The 1,4-phthalazinedione 75 was generated according to a reported procedure⁴⁹. It was not isolated, but reacted in situ. Addition of the diene 72 to the greenish solution of 75 caused immediate color discharge. The reaction was allowed to warm up to room temperature, at which time water was added to the solution. The organic layer was separated and combined with methylene chloride washings of the water layer. The combined extracts were dried over sodium sulphate, filtered and the solvent removed leaving a white solid (55% yield); m.p. 188 - 189°C; IR: 3040, 1750, 1670, 1640, 1610, 1400, 1315, 1270, 1130cm⁻¹;

nmr (CDCl_3). .95 - 1.35 (2CH_3 , 2t), 3.35 - 3.70 (2CH_2 , 2q), 5.65 - 5.7 (CH, m), 6.65 - 6.7 ($=\text{CH}$, m), 7.7 - 8.0 (ring CH, m), 8.2 - 8.45 (ring CH, m).

Anal. Calcd for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_4$: C, 64.96; H, 5.77, N, 8.91.

Found; C, 64.92; H, 5.68; N, 8.98.

Reduction of Diels Alder adduct 76 to 77

To 1.5 g of the olefin 76 in 15 mL of absolute ethanol was added a catalytic amount of palladium on charcoal. The mixture was placed in a hydrogen atmosphere and in 5 minutes, 1 equivalent of hydrogen had been absorbed. The charcoal was filtered off and the ethanol removed in vacuo, leaving a white solid (77) in 86% yield; m.p. 186 - 187°C; IR: 3025, 1635, 1610, 1405, 1395, 1330, 1130, 1090 cm^{-1} ; nmr (CCl_4) .90 - 1.45 (2CH_3 , 2t), 1.7 - 2.5 (CH_2CH_2 , q), 3.4 - 3.9 (2CH_2 , 2q), 5.05 - 5.2 (CH, s), 7.6 - 8.05 (ring CH, m), 8.15 - 8.5 (ring CH, m).

Anal: Calcd for: $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}_4$: C, 64.54; H, 6.37; N, 8.85

Found: C, 64.53; H, 6.58; N, 8.84.

Treatment of 77 with sodium hydroxide

A mixture of 1 g of 77 in 25 ml of 10% sodium hydroxide was refluxed for 3 hours. After the refluxing period the solid amide was still present as an insoluble precipitate which was recovered. No reaction had occurred.

The amide (.5 g) was refluxed in ethylene glycol the presence of potassium hydroxide for 4 hours. No products other than starting material were isolated.

Reaction of amide 77 with disiamylborane

The amide 77 was treated with 2 equivalents of disiamylborane according to a reported procedure⁶⁹. A glc analysis of the product showed 5 major peaks which were not characterized.

Reaction of amide 77 with sodium bis(2-methoxyethoxy) aluminium hydride

To .64 g (.002 mole) of the amide 77 in 25 ml ether at 0°C, 2.1 equivalents of the aluminium hydride (Vitrade) was added. The solution was stirred at 0°C for 1 hour, and then allowed to warm up to room temperature. To the solution 5 ml water was added, the organic layer was then separated, and dried over sodium sulphate. The solvent was removed in vacuo, leaving a thick oil; nmr (CCl₄), 1.0 - 1.4 (2CH₃, m), 1.6 - 2.3 (CH₂CH₂, m), 3.1 - 4 (m), 6.9 - 7.35 (ring H, m), 7.6 - 8.3 (ring H, m); IR: (CHCl₃), 1695, 1635, 1610, 1320, 1090cm⁻¹.

It was obvious from the nmr and IR, that only part of the amide was reduced. The reduction product was 79 and not 78 as seen by the presence of the phenyl groups.

The amide 77 was then reduced in 92% yield to the dibenzylamine 79 with lithium aluminium hydride. nmr (CDCl₃), 1.0 - 1.45 (CH₃, m), 1.6 - 2.2 (CH₂CH₂, m), 3.9 - 4.0 (m), 6.85 - 7.35 (ring H, m).

The benzylamine 79 was dissolved in an acetic/trifloro-

acetic acid mixture, to which a catalytic amount of palladium on charcoal was added. There was no hydrogen uptake after 3 days.

Ethyl azodicarboxylate 83a

The azo 83a was prepared by oxidation of the hydrogen precursor according to a reported procedure⁶⁸; IR: 3020, 1785, 1375, 1240, 1030 cm^{-1} ; nmr (CDCl_3), 1.45 (CH_3 , t), 4.48 (CH_2 , q).

Reaction between ethyl azodicarboxylate and 72

To 5.7 g (.037 mole) of the diene 72 in 200 ml of pentane, was added 6.3 g (.037 mole) of the azo 83a. After stirring the solution for 1 hour, the solvent was evaporated and an orange oil remained (11.1 g). The oil was poured through a chromatographic column (silica gel) with chloroform as eluent. Several fractions were collected. The first few fractions were unreacted azo 83a (nmr). The next fractions were a mixture of azo 83b with the required adduct 84a. The following fractions were mixtures of 84a and dimer of 72. The required adduct was obtained in calcd. 9% yield; nmr, (CDCl_3), 1.0 - 1.6 (4CH_3 , m), 3.2 - 3.8 (2CH_2 , m), 4.0 - 4.9 ($2\text{CH}_2, 2\text{CH}$, m), 6.47 - 6.7 ($=\text{CH}$, m).

Reaction of methyl azodicarboxylate 83b with 72

The methyl azodicarboxylate was prepared according to a reported procedure⁶⁸.

To a solution of the azo 83b (130 g - .89 mole) in

300 ml of ether at 32°C was added dropwise 600 ml of pentane at -78°C containing 35 g (.228 mole) of the diene 72.

After the addition was completed, the solution was dried over sodium sulphate, filtered, and the solvent evaporated.

in vacuo. The excess azo 83b was distilled off (39°C at 1.5 mm) leaving a thick oil which was passed through a

chromatographic column to rid it of traces of 83b. The

purification did not succeed in separating the mixture. To

facilitate the purification, the mixture of 83b and 84b

was reduced with palladium on charcoal in absolute ethanol.

After filtering the charcoal, and evaporating the ethanol

(in vacuo), the oil was taken up in carbon tetrachloride

and washed with water several times. The azo 83b which was

reduced to the hydrazo (water soluble) was eliminated

completely. A glc analysis (8' -20% Se30 at 250°C) of the

residual oil showed only two peaks (67% and 33%). The

larger peak was the desired product 85 in 30% overall yield:

IR: 3000, 2980, 1735, 1460, 1360, 1325, 1275, 1130, 920cm⁻¹;

nmr. 1.0 - 1.4 (2CH₃, 2t), 1.6 - 2.0 (CH₂CH₂, m), 3.3 - 3.8 (2CH₂, q), 3.178 (CH₃, s), 4.0 - 4.45 (CH, m).

The second peak was identified as the reduced dimer

of 72; nmr. 1.1 - 1.35 (CH₃, t), 1.4 - 2.8 (m),

3.3 - 3.7 (CH₂, q).

Hydrolysis of 85 to 86

A solution of 1 g of ester 85 in 25 ml of methanol/

6

KOH (25%) was refluxed for 3 hours. The solution was neutralized with dilute hydrochloric acid, and evaporated in vacuo to a thick oil which was taken up in chloroform. The nmr of this oil was identical with starting material.

The reaction was carried out again on 2.6 g (.009 mole) of the diester 85 in 15 ml of 25% ethylene glycol/KOH solution. The solution was heated to 120°C for 12 hours, after which time a strong characteristic amine smell was observed. The reaction mixture was cooled and 10 ml of water was added. Ether extractions were carried out on the mixture. The ether extracts (3 x 50 ml) were dried over potassium carbonate, filtered, and the ether removed in vacuo leaving a dark liquid; IR 3400-3200, 2950, 1130, 1090cm⁻¹; nmr (CDCl₃), 1.0 - 1.4 (CH₃, m), 1.4 - 2.1 (m), 3.2 - 4.1 (m).

The spectral data seemed to agree with the structure of the desired hydrazo. However, several attempts to reproduce the latter results were not very successful.

The hydrolysis was accomplished by heating (100°C) 11 g of the ester 85 in 25% aqueous KOH, for 20 hours. Ether extractions (4 x 100 ml) were carried out on the aqueous solution. The ether extracts were dried over sodium sulphate, filtered, and the solvent evaporated. The residual liquid was composed of several components (glc), of which the major was the azo 86 (33% yield): IR: (CDCl₃) 2995, 2240, 1330, 1200, 1150, 1090, 1050cm⁻¹; nmr (CDCl₃),

.08 - 1.4 (2CH_3 , m), 1.6 - 2.3 (CH_2CH_2 , m), 3.2 - 3.7 (2CH_2 , m), 4.9 (CH, m).

Reduction of 86 to 80

A solution of 1.3 g of the azo 86, 25 ml of 95% ethanol and a catalytic amount of palladium on charcoal was kept under a hydrogen atmosphere. There was a rapid absorption of one equivalent of hydrogen, followed by a very slow absorption of a second equivalent. The charcoal was filtered, and the ethanol evaporated in vacuo, leaving a pale yellow liquid which darkened rapidly upon exposure to air. Recovered 1.1 g (85%) of the product 80: IR: 3300, 3180, 2990, 1140, 1060cm^{-1} ; nmr (CDCl_3), 1.0 - 1.5 (2CH_3 , 2t), 1.5 - 2.2 (CH_2CH_2 , m), 2.4 (2NH_2 , broad s), 3.1 - 3.4 (2CH, m), 3.3 - 3.9 (2CH_2 , 2q).

Reaction of 80 with p-toluene sulfonyl chloride

To .5 g (.028 mole) of the diamine 80 in 25 ml of chloroform was added .5 g of triethyl amine and 1.1 g (.058 mole) of p-toluene sulfonyl chloride. On mixing the amine and the chloride, a slight amount of heat was generated. The mixture was refluxed for 1 hour after which time the solution was cooled and the solvent evaporated in vacuo. The residual redish liquid was stirred vigorously with petroleum ether and the precipitate which had formed was filtered. This solid was then taken up in chloroform. Several water washings of

the chloroform were carried out in order to eliminate the triethylamine hydrochloride. The chloroform was then evaporated in vacuo, leaving a pale yellow solid (.85 g-61%); m.p. 118-119°C; IR: 3360, 3310, 3040, 2990, 2940, 1605, 1450, 1400, 1350, 1160, 1090, 940cm⁻¹; nmr (CDCl₃), 0.85 - 1.4 (2CH₃, m), 1.3 - 1.65 (CH₂CH₂, m), 2.4 (ring CH₃, s), 2.9 - 3.6 (m), 7.1 - 7.3 (ring CH, d), 7.55 - 7.7 (ring CH, d). Anal: Calcd. for: C₂₁H₃₃N₂S₂O₆; C, 55.62; H, 6.50; N, 5.64. Found: C, 55.78; H, 6.81; N, 5.64.

Hydrolysis of 88 to 89

A mixture of .5 g (.001 mole) of 88 in 25 ml of 10% HCl was refluxed for 12 hours. The precipitate was filtered off and dried in a vacuum oven to give the ketone in 100% yield as a white solid; m.p. 145 - 146°C; IR: 3440, 3340, 3280, 3040, 1710, 1605, 1350, 1230, 1165cm⁻¹; nmr (CDCl₃), 2.2 - 2.65 (CH₂CH₂, m), 2.4 (CH₃, s), 5.0 - 5.3 (NH, m), 6.8 - 7.1 (2CH, t), 7.1 - 7.35 (ring CH, m), 7.5 - 7.85 (ring H, m).

Cyclization of 81 with vinyltriphenylphosphonium bromide

To .1 g (.0024 mole) of 81 in 25 ml of dry ether under nitrogen was added .006 g of sodium hydride (1.2 equivalents). The solution was refluxed for two hours and then .088 g (.002 mole) of the vinyl salt was added. The solution was stirred at room temperature for an

additional 2 hours. The solvent was then evaporated in vacuo and the solid which remained was passed through a small chromatographic column (alumina) to eliminate the triphenylphosphine oxide. The column did not separate the product from the triphenylphosphine oxide. Because of the small amount of solid involved, further purification was not attempted; IR: 3400, 3250, 3040, 1600, 1440, 1340, 1160 cm^{-1} ; nmr: 2.2 - 2.7 (CH_2CH_2 , m), 2.4 (CH_3 , s), 2.9 - 3.55 (CH_2CH_2 , 2t), 7.0 - 7.8 (ring CH, m).

A total of .1 g was collected from the chromatographic column. The yield of product 91 was calculated to be 48%, based on nmr integration.

References

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PART II

SYNTHETIC APPROACHES TO CIS- γ -BISABOLENE

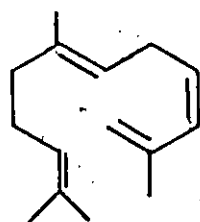
INTRODUCTION

Terpenes are fragrant, easily isolated plant constituents which have intrigued organic chemists for ages. The vast amount of chemistry which has been done with compounds of this type has provided exhaustive information about a large variety of reactions. For instance, structural effects on carbonium ion rearrangements have been largely investigated with compounds of this type^{1,2}. Also, biogenetic theories for terpene formation were among the first to be proposed and investigated. Since most terpenes can be subdivided into five-carbon segments, early biogenetic theories for their formation were centered around the "isoprene rule"³. Support for this theory was derived from the isolation of isoprene from the pyrolysis of natural rubber and limonene³. However, recently it has been firmly established that not isoprene, but isopentenyl pyrophosphate derived from mevalonic acid is the active intermediate⁴.

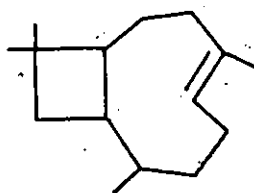
Terpenes are classified in groups which are multiples of the basic C_5H_8 unit.

Monoterpenes	$C_{10}H_{16}$
Sesquiterpenes	$C_{15}H_{24}$
Diterpenes	$C_{20}H_{32}$
Triterpenes	$C_{30}H_{48}$
Tetraterpenes	$C_{40}H_{64}$
Polyterpenes	C_5H_8n

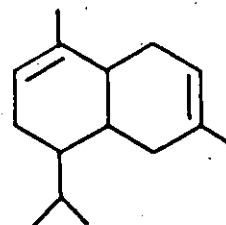
Structures vary immensely from unsubstituted acyclic systems to complex multifunctional polycyclic systems. For example, some common sesquiterpenes are illustrated in Fig.1.



FARNESENE



CARYOPHYLLENE



CADINENE

Fig. 1. Common sesquiterpenes

Bisabolene

Bisabolene falls into the category of sesquiterpenes with the formula $C_{15}H_{24}$. After cadinene and caryophyllene, it is the most widely distributed sesquiterpene. Bisabolene was first isolated from bisabol myrrh by Tucholka⁵ in 1897. Burgess and Page⁶ isolated bisabolene from the oil of limes and called it limene. They also found limene in the oil of bergamot⁷ and characterized it by making the trihydrochloride which melted at $79-80^{\circ}$. Bisabolene could be regenerated from the trihydrochloride by reacting it with sodium acetate-acetic acid mixture⁶. For the next twenty years, the presence of limene was detected by formation of this trihydrochloride. In 1924 Ruzicka⁸ investigated bisabolene

isolated from bisabol myrrh and found it to give the same trihydrochloride as limene. He found that limene and bisabolene were identical, the latter now being the established name. Ruzicka postulated the structure of bisabolene from work done on cyclization of α - and β -farnesene obtained from dl-nerolidol (Fig.2). The cyclization could give three products of the bisabolene type labelled α , β and γ which were all capable of producing the same trihydrochloride derivative from which bisabolene could be generated.

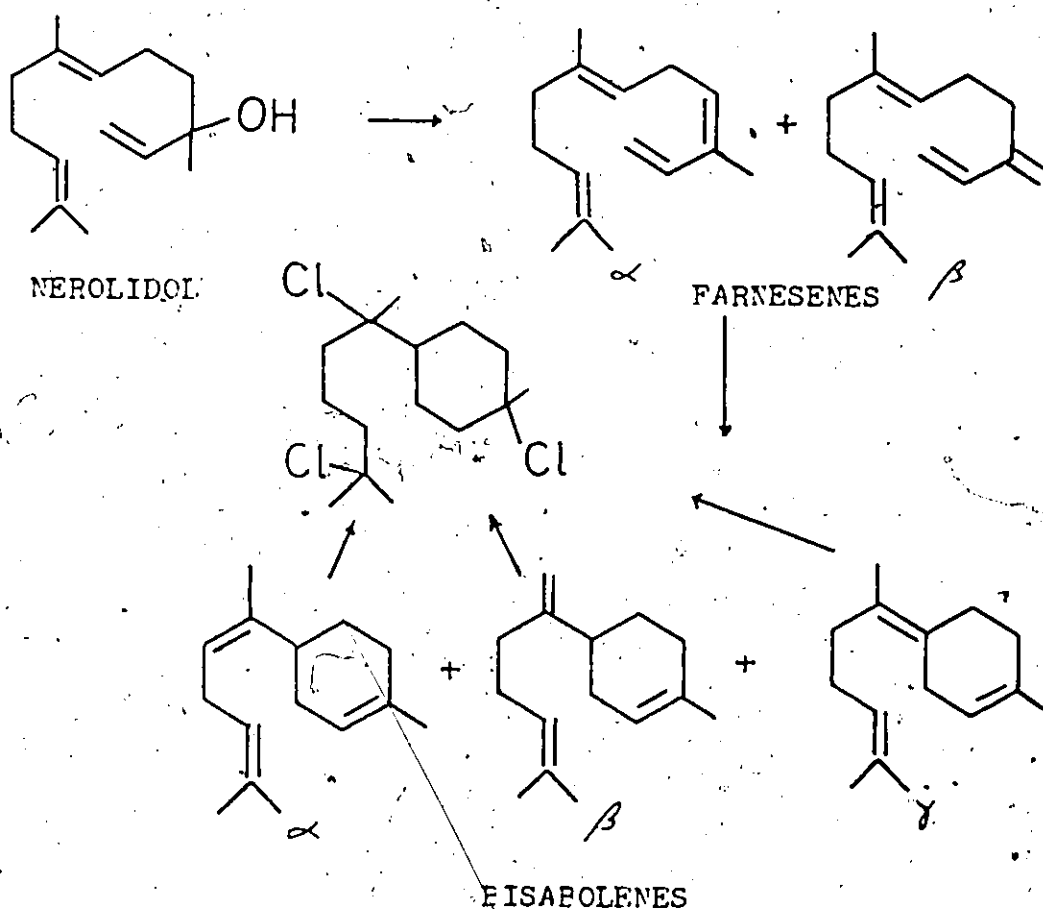


Fig. 2 Farnesene cyclization

Ozonolysis⁹ of regenerated and natural bisabolene gave acetone, levulinic acid and succinic acid. These products could be obtained from the fragmentation of α -or γ -bisabolene as outlined below (Fig.3).

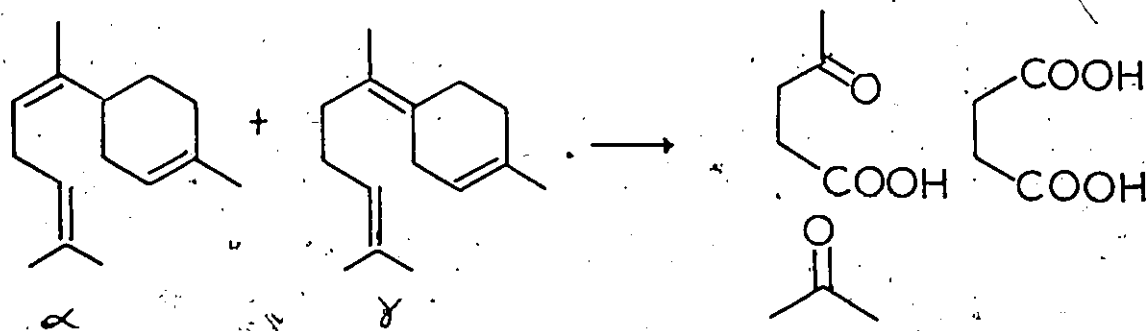
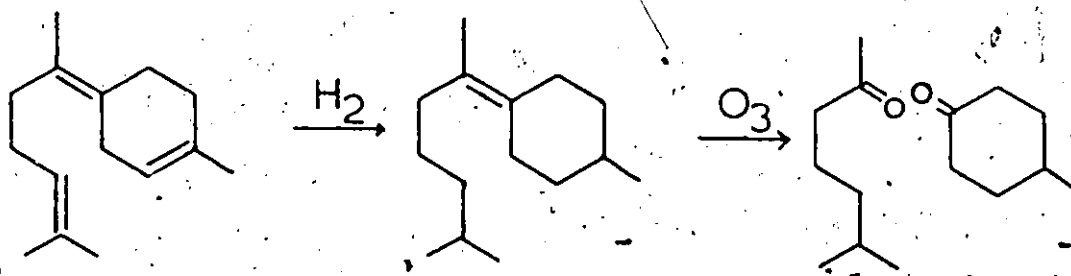


Fig. 3 Ozonolysis of bisabolene

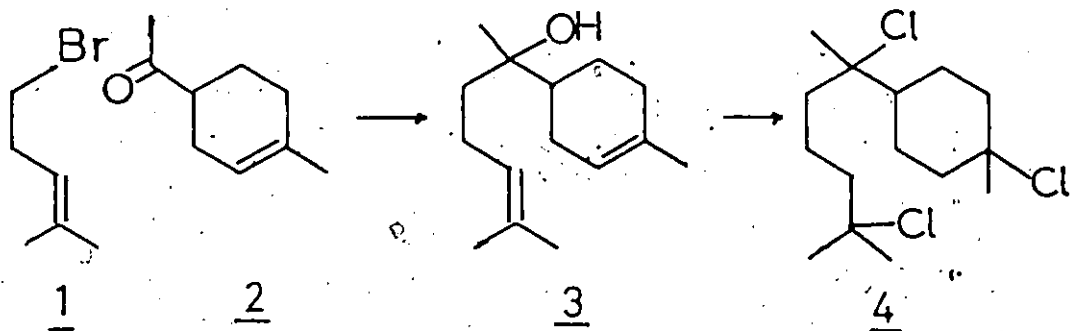
The α -bisabolene could produce some of these products only with very complete degradation. The complete absence of formaldehyde or formic acid showed that the β form was not present. Hydrogenation of bisabolene in cyclohexane solution with platinum black gave tetrahydrobisabolene¹⁰. On ozonolysis⁹ this hydrocarbon produced a mixture of 6-methyl-2-heptanone and 4-methylcyclohexanone. This was proof of the position of the olefinic linkage and that the γ isomer was isolated.



When β -bisabolene was subsequently isolated^{11,16} it was found to give the same trihydrochloride and on regeneration of the bisabolene gave the γ -isomer. All three forms of bisabolene have been isolated¹² from natural sources and in one instance all seem to be present in the same plant¹³.

Bisabolene Synthesis

The first synthetic work on γ -bisabolene was carried out by Ruzicka¹⁴. A Grignard reaction between 2-methyl-5-bromopent-2-ene (1) and 1-methyl-4-acetylcyclohexene (2) gave bisabolol (3). The trihydrochloride formed from natural bisabolene and regeneration of γ -bisabolene was



carried out in the usual manner. The β -isomer has been synthesized several times as a racemic mixture¹⁵. The natural β -bisabolene has been isolated as the l-enantiomer¹⁶ which is another instance of biogenetic selectivity. The

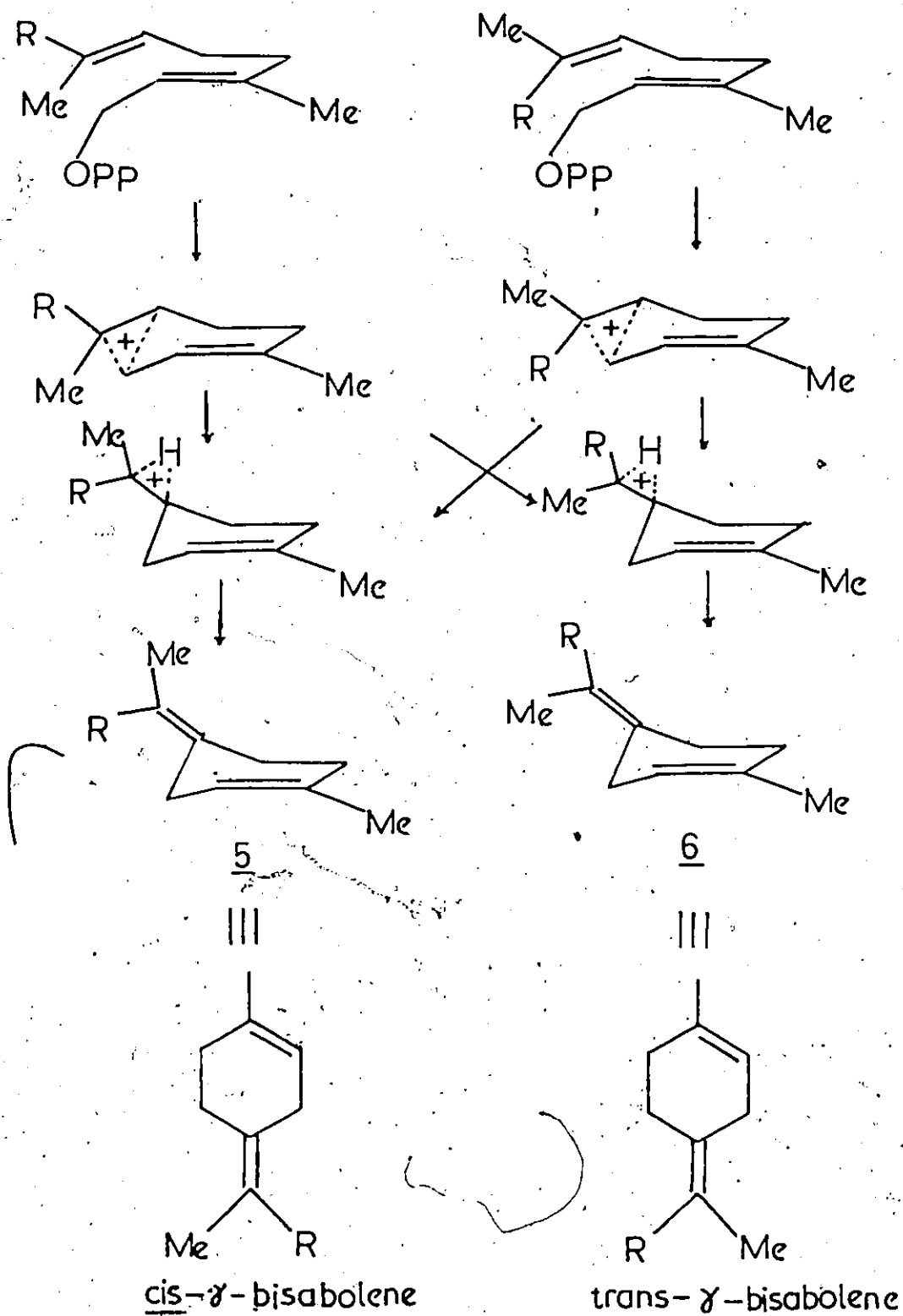


Fig. 4 cis and trans- γ -bisabolene synthesis

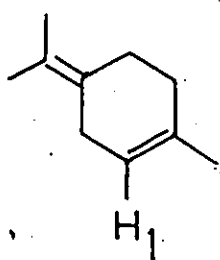
α -isomer has also been isolated¹⁷ but to date has not been synthesized.

cis and trans γ -Bisabolene

In a paper on the biogenesis of γ -bisabolene, Ruzicka¹⁸ proposed a sequence of reactions which produced two geometrical isomers (Fig. 4). Before this time the possible existence of two isomers of γ -bisabolene had not been recognized. The scheme starts with two possible forms of farnesyl pyrophosphate, a known intermediate in terpene biosynthesis, and leads to the formation of cis and trans γ -bisabolenes. Of interest is the fact that there is a cross-over point in the two syntheses and either of the two farnesyl derivatives could give cis or trans products. The selectivity known to exist in most biosyntheses makes it probable that only one of the isomers is generated and in order to verify the biogenetic theory, the structure of the natural γ -bisabolene must be determined.

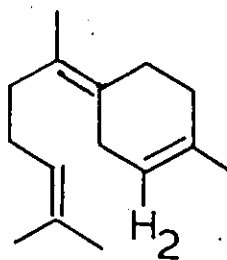
The similarity of the two structures 5 and 6 renders separation a formidable task. Minyard¹⁹ isolated a γ -bisabolene from smooth leaf cotton buds (*Gossypium Lirsutum*) and assigned it the cis- γ -bisabolene configuration (5). This assignment was based on a comparison of the nuclear magnetic resonance (nmr) signals of bisabolene and terpinolene (7). The ring vinyl proton signal (H_2 - 5.26) in the bisabolene was shifted 0.03 ppm upfield from the corresponding signal (H_1 , -5.29) in terpinolene although the methyl protons differ

by only 0.007 ppm. Minyard attributed the differences in chemical shifts of vinyl protons to a shielding effect by the side chain in the cis- γ -bisabolene to the "near side"



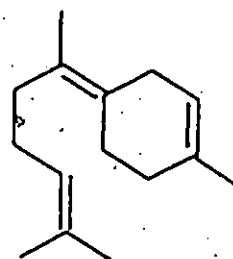
terpinolene

7



cis

5



trans

6

vinyl proton (H_2). The author admitted that there could be other reasons (ie. dilution errors, temperature change, etc.) responsible for the observed phenomenon. The infrared spectrum of the pure "cis"- γ -bisabolene differs from that of regenerated bisabolene as expected, because the latter would necessarily be a mixture of isomers.

The only conclusion that can be drawn from the above data is that one of the γ -bisabolene isomers has been isolated but its structural assignment is uncertain. Conclusive determination of the cis-or trans-configuration to γ -bisabolene can be best made by comparison with a stereospecifically synthesized sample.

RESULTS AND DISCUSSION

The diagram in Fig.5 outlines the scheme proposed for the synthesis of cis- γ -bisabolene. The reaction sequences

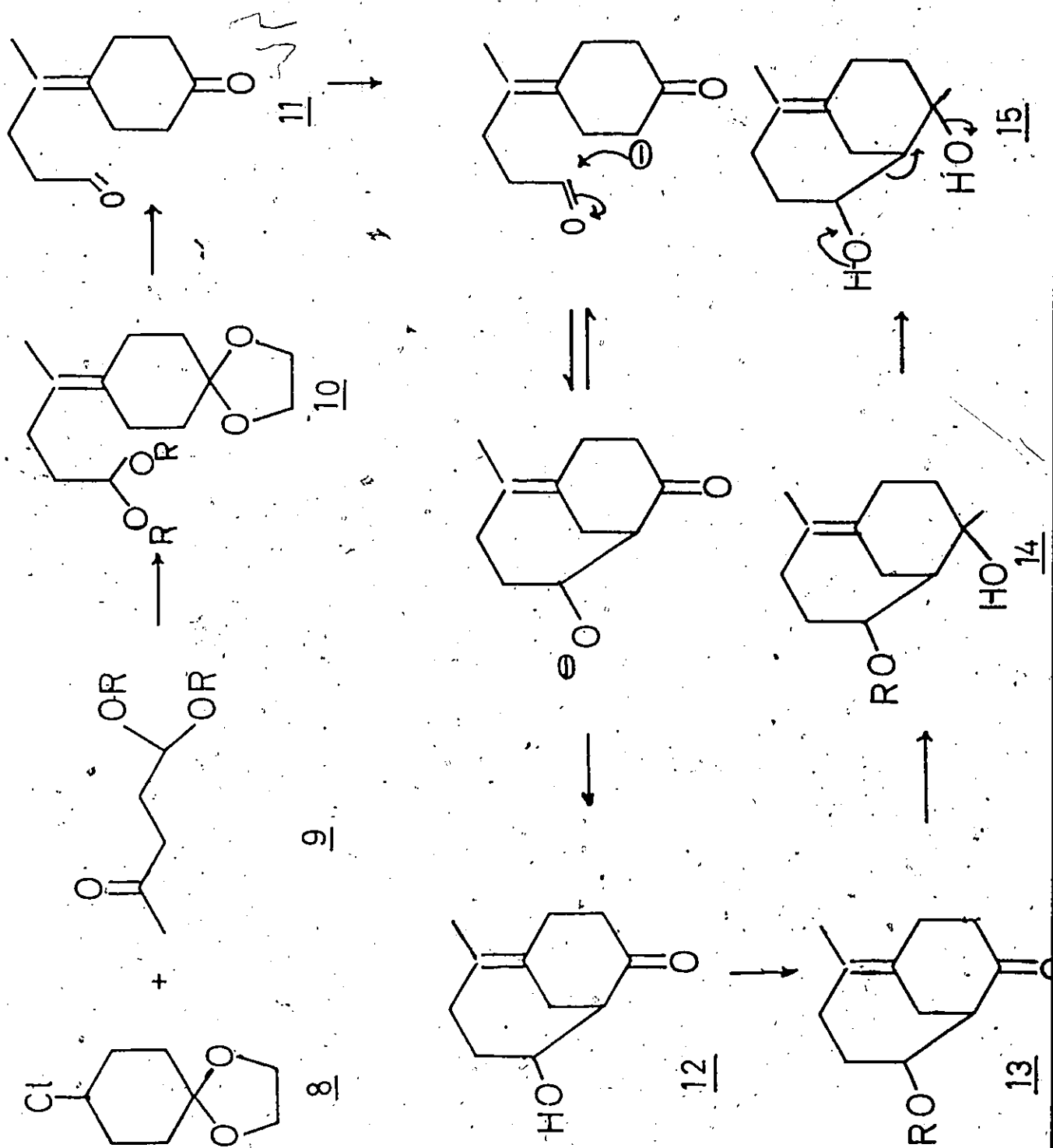
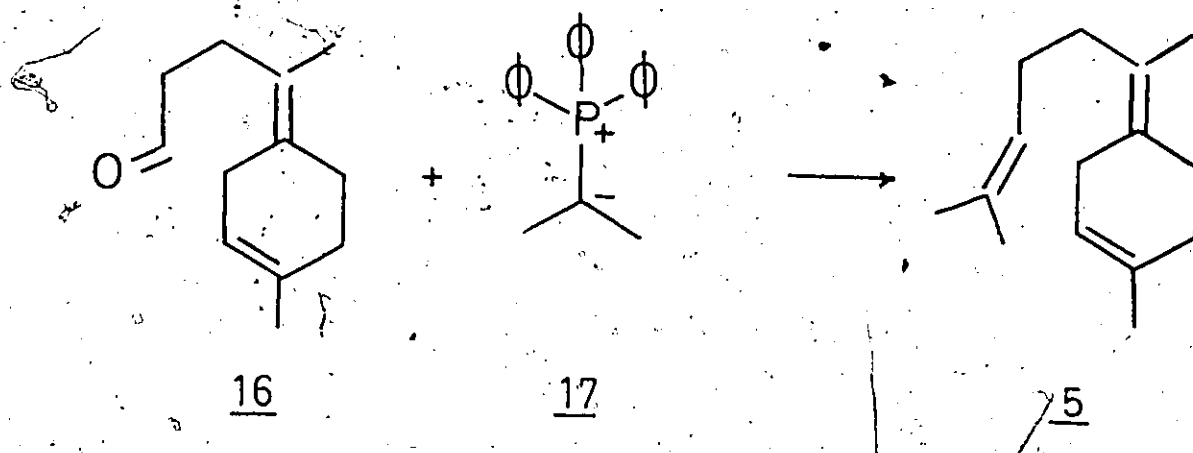


Fig. 5 "*cis*- γ -bisabolene" proposed synthetic scheme

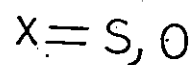
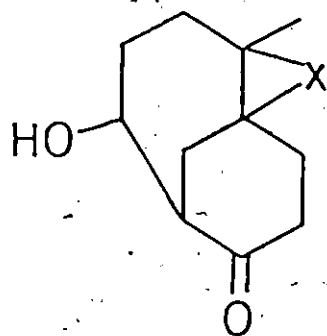
are designed around the fragmentation of the tertiary alcohol 15 to give a "cis" relationship between the olefinic linkage and the side chain. Breaking of the strained bicyclic system would be a driving force for the desired fragmentation. The aldehyde function thus produced in 16 would then be treated with 2-propyltriphenylphosphorane (17) in a Wittig reaction to generate pure cis-1-bisabolene.



Formation of the diol 15 could be accomplished by a Grignard reaction on the protected ketoalcohol 13 with methylmagnesium iodide. The bicyclo[4.3.1]decane system (12) could be obtained via an intramolecular aldol condensation of the ketoaldehyde 11. The formation of bicyclic systems by intramolecular aldol condensations are common²⁰, but the formation of the bicyclic system containing the bridgehead olefin would be difficult. Dehydration of the alcohol produced is also a factor to be considered.

Models show that removal of the carbon-carbon double

bond by formation of an epoxide or episulphide (18) would relieve the strain in the ring and allow the cyclization to proceed. The advantage of episulphides is that the



18

olefin can be regenerated stereospecifically by desulfurization using triphenylphosphine²¹ (Fig.6). Regeneration of a hydrocarbon from the epoxide²² results in inversion of the olefin stereochemistry and would provide a route to trans- γ -bisabolene (6).

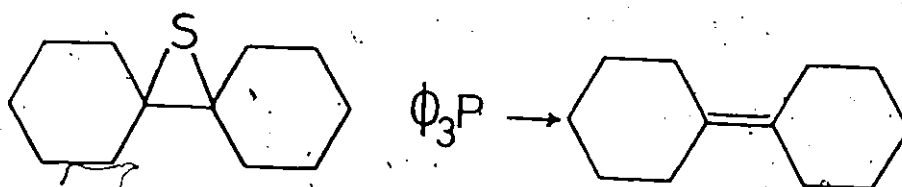


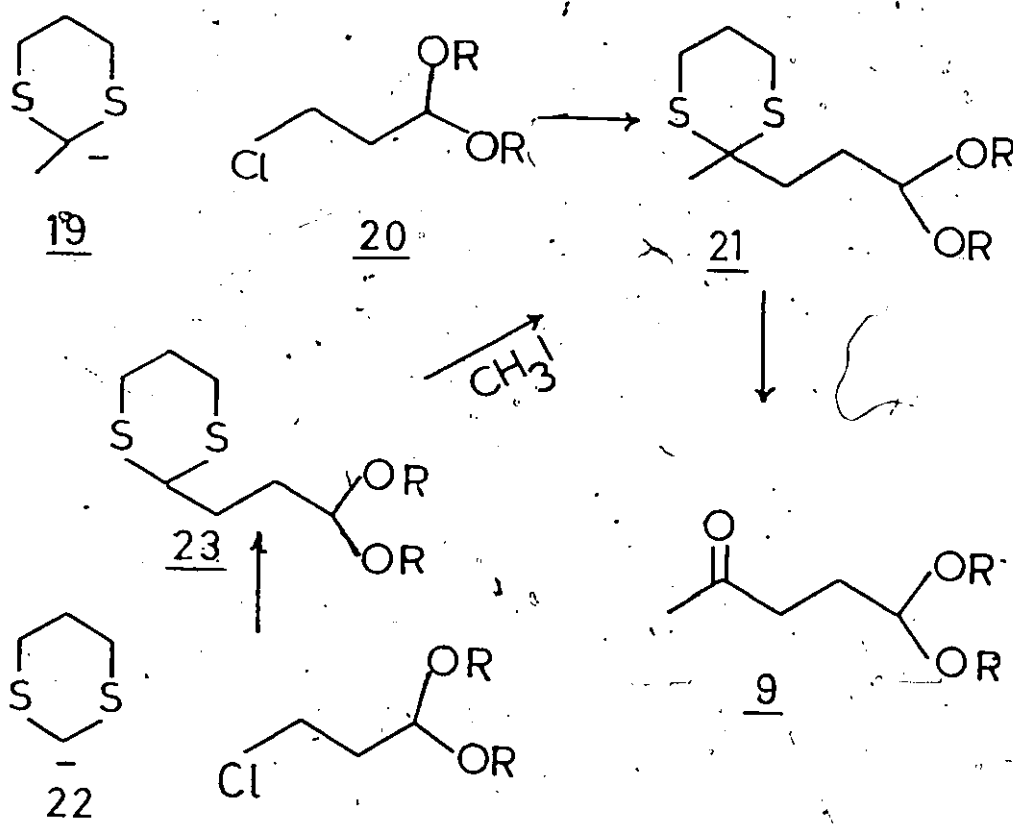
Fig. 6 Reaction of triphenylphosphine on episulphides

Synthesis of the diketal 10 could be accomplished by

Wittig reaction between the triphenylphosphonium salt of 8 and 1,1-dialkoxy-4-pentanone (9).

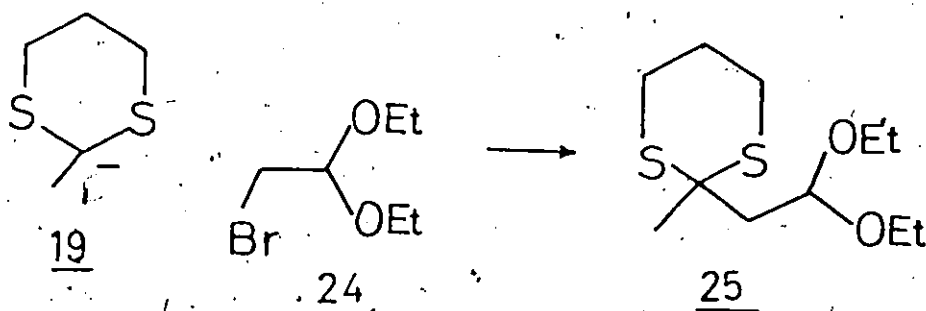
Synthesis of 1,1-dialkoxy-4-pentanone

Corey's dithiane method²³ for generating ketones was initially used in an attempt to obtain 1,1-diethoxy-4-pentanone (9). The ability of dithiocarbanions, generated from



dithianes, to react with halides in nucleophilic displacements is well documented²³⁻²⁵, consequently the reaction between the dithiane anion 19 and β -chloropropionaldehyde diethyl acetal 20 to produce 21 was anticipated. The conversion of this thioacetal to the required ketone 9 would be

accomplished with the use of mercuric chloride/mercuric oxide mixture in an aqueous medium. Attempts to obtain 21 were unsuccessful under all conditions tried. The addition of sodium bromide did not alter the outcome. In most cases the starting materials were recovered. Possible steric hindrance of the anion to approach of the chloride led to the use of unsubstituted dithiane 22. The reaction product expected (23) could give the desired product 21 by methylation of the anion of 23 with methyl iodide. Unfortunately the unsubstituted dithiane 22 also



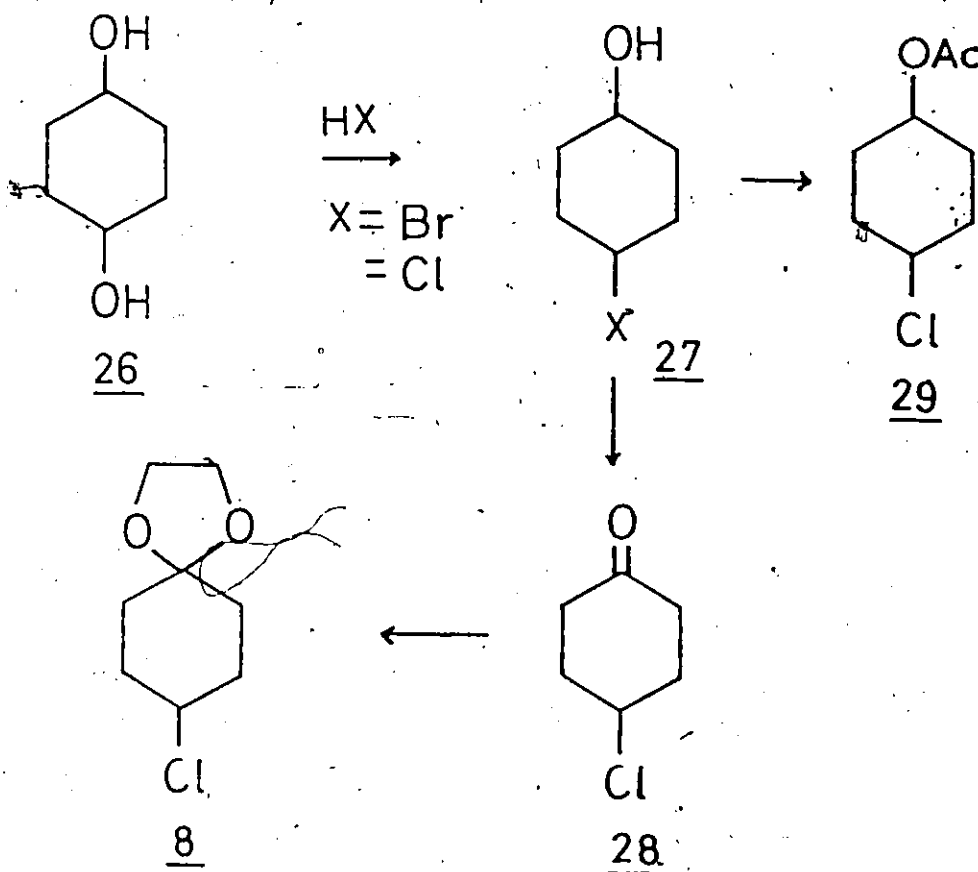
would not react with the chloride. To verify the techniques 2-methyl-1,3-dithiane anion (19) was reacted with 2-bromoacetaldehyde diethyl acetyl (24). The reaction took place to yield the adduct 25. The ability of the anion to displace the bromide but not the chloride, reflects the poor leaving group character of the chloride ion. These results are in agreement with the results of

Meyers²⁶ who has achieved similar reactions using dihydro-1,3-oxazine anions to displace halides.

The preparation of the required ketone 9 was accomplished by cleavage of 2-methylfuran²⁷ to give the product directly. The reaction was carried out with ion exchange resin and gave the product in 10-20% yield. Better yields have been reported²⁸ with the use of alcoholic HCl.

Synthesis of 4-chlorocyclohexanone ethylene ketal (8)

Synthesis of chloro ketal 8 was carried out according to the proposed scheme below. Cyclohexane-1,4-diol (26)



was reacted with concentrated HCl to produce 4-chlorocyclohexanol (27) (cis-and trans-mixture) in 20-40% yield³⁹.

Preparation of the bromide, was attempted, but even lower yields were obtained due to a large amount of olefinic (nmr) side products.. An alternate preparation of the haloalcohols is the reaction of 1,4-epoxycyclohexane with the respective acids. The yield of halide in the latter case is higher (65%), but the overall yield in two steps from 1,4-cyclohexanediol is not improved^{29,30}. Oxidation of the chloroalcohol (27) with chromium trioxide/acetone (Jones reagent) produced the chloroketone 28 which was converted to the chloroketal 8 in the usual manner. Several attempts at reacting triphenyl phosphine with 8 to produce the phosphonium salt were unsuccessful. The reaction was also tried with 4-chlorocyclohexyl acetate (29) without success. This was unexpected as the reaction between triphenylphosphine and bromocyclohexane produced the phosphonium salt in high yield³¹ (94%). It is felt that in the chlorocyclohexyl system, an elimination reaction is taking place. The isolation of a high melting solid with no cyclohexyl protons in the nmr supports this postulate.

Elimination reactions of alkyl halides with triphenylphosphine to form triphenylphosphine-H-X and an olefin have been observed³² and attributed to the basic character of triphenylphosphine. The halide salts produced are capable

of reacting with olefins. This type of reaction may be taking place in the bromocyclohexane system, but is unacceptable for obtaining the desired phosphonium salt because of the possibility of forming two isomers (Fig. 7) which consequently results in isolation difficulties.

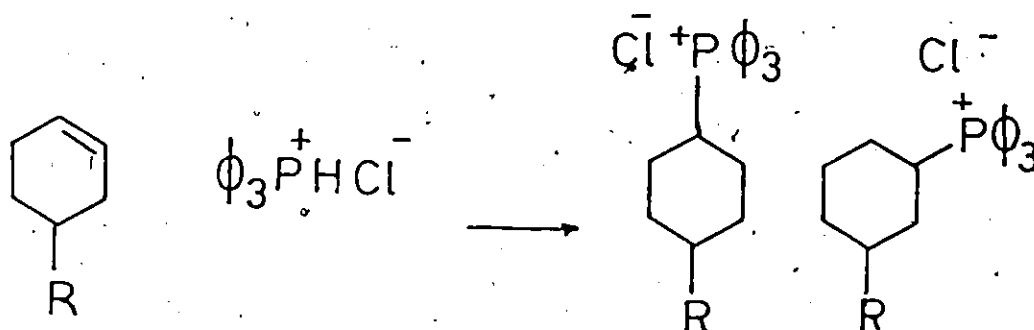


Fig. 7 Possible reaction between phosphonium salt and substituted cyclohexene

Because of the difficulty in forming the phosphonium salt in the cyclohexyl system, interest was generated in an alternate scheme in which the phosphonium salt of γ -bromovaleraldehyde diethyl acetal (31) was reacted with the ketone 32 to produce the required product 10 (Fig. 8). Unfortunately it was found that triphenylphosphine eliminates HBr in the bromide 30³³. The triphenylphosphine hydrobromide formed did not react with the olefin generated, but rather with the acetal group to give ethyltriphenylphosphonium bromide. A similar reaction has been observed upon reacting triphenylphosphine hydrobromide with γ -hydroxyvaleraldehyde diethyl acetal³³ (Fig. 8).

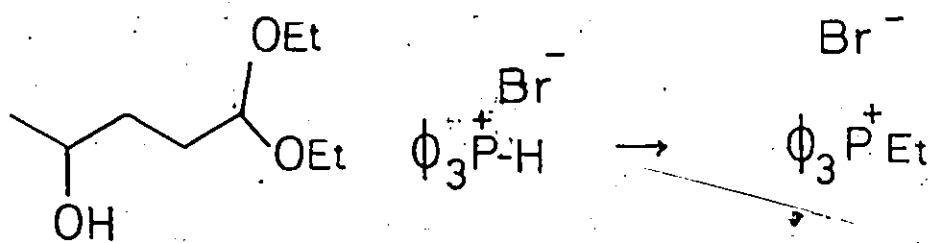
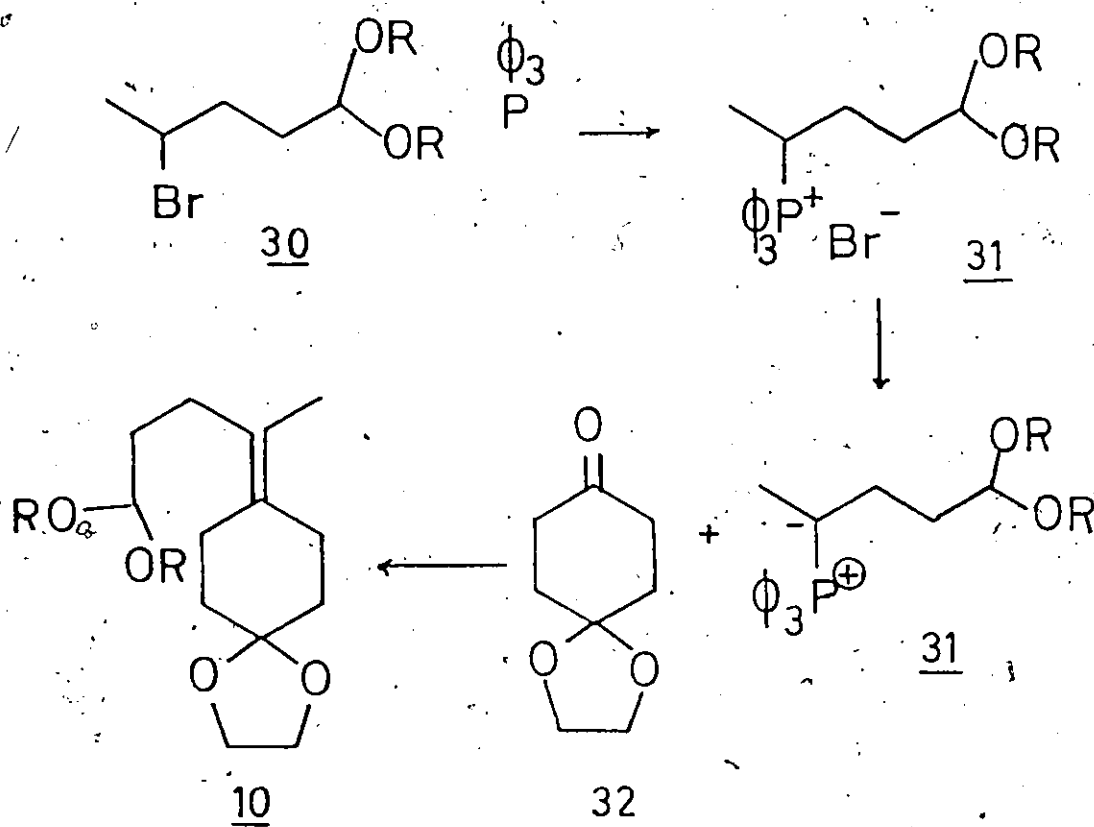
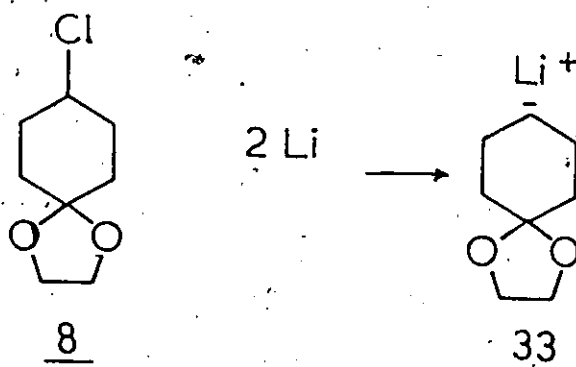


Fig. 8 Reaction of phosphines with secondary
substrates

The solid obtained from the reaction of triphenylphosphine and the chloride 8 is possibly the product of a similar reaction of triphenylphosphine hydrochloride with the ketal. Because of these difficulties, use of the Wittig reaction as a means of incorporating the tetrasubstituted double bond has been abandoned.

Work was directed towards alternative methods of combining the two fragments 8 and 9. Attempts to produce the cyclohexyl lithium system 33 which would react with the



ketoacetal 9 were also unsuccessful. The Grignard reaction was then used with some success to combine the two fragments. Initial difficulties encountered in making the Grignard reagent of chloroketal, 8 were overcome by using higher boiling solvents. Low yields of the product 35 were obtained, due to self destruction of the Grignard reagent, possibly by attack of the reagent 34 on the ketal function. Reactions of Grignard reagents with ketals have been observed³⁴ and

alcohols are formed in high yields (Fig.9). Addition of

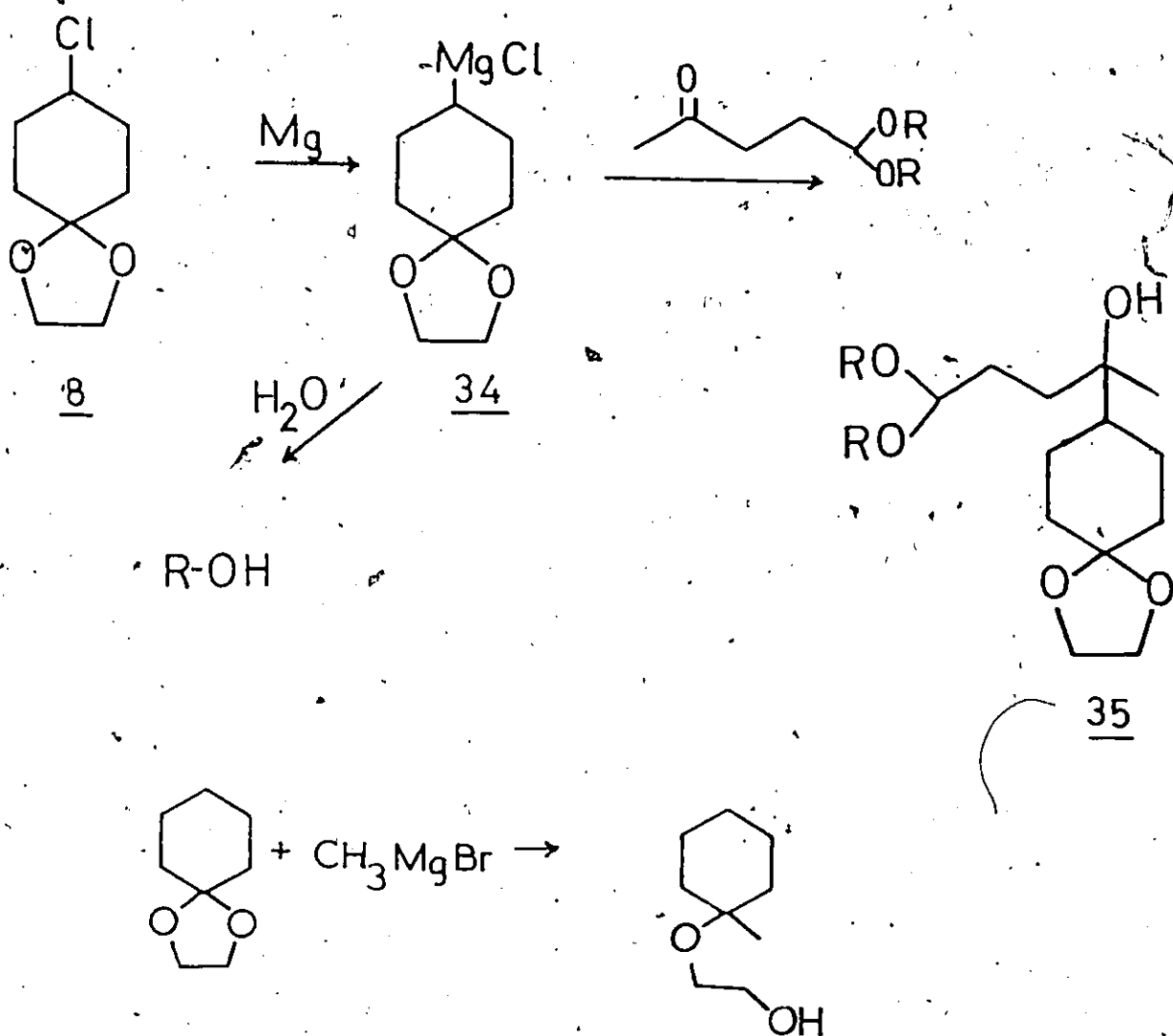


Fig. 9 Reaction of Grignard reagent with ketals

water to an aliquot of the reagent 34 generated from the chloroketal 8 also gave a small amount of unidentified alcohol. The presence of this alcohol may be an indication of the ketal opening taking place and accounts for the low yield of alcohol 35.

Because of the low yield of the desired alcohol 35 the project was stopped at this point. It was felt that a different approach was needed.

EXPERIMENTAL

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected; boiling points are uncorrected. Vapor phase chromatography (v.p.c.) analyses were carried out on a F&M Model 720 Gas Chromatograph. Nuclear magnetic resonance (nmr) spectra were obtained using a Jeol Model C-60 HL spectrometer and are expressed in p.p.m. downfield from tetramethylsilane as an internal standard. Infrared spectra were determined with a Beckman IR-12 and IR-10 and were run in chloroform solutions unless otherwise indicated. Tetrahydrofuran was distilled from lithium aluminium hydride prior to use.

2-methyl-1,3-dithiane 19

The dithiane was prepared by the two methods outlined by Corey²³, in 70% yield; b.p. 70-71°C (6mm); $n_D^{24} = 1.5597$; (Lit.²³ 79-80, 8-10mm); IR (CS₂) 1420, 1275, 1190, 910, 720, 680 cm^{-1} ; nmr (CDCl₃) 4.0 - 4.3 (CH₃, d, J=7), 1.45 - 1.55 (H, q, J=8), 2.66-3.03 (2SCH₂, m), 1.66-2.36 (CH₂, m)

2-methyl-2-(3,3-diethoxy propane)-1,3-dithiane

A solution of 4.02g (0.03mole) of 2-methyl 1,3-dithiane and 100 mls of tetrahydrofuran was cooled to -23°C (CCl₄/Dry Ice). To the cooled solution 14.5 mls (0.03 mole) 14.5% n-butyl lithium (Foote Mineral Co.) was added dropwise. After the addition was completed, 5g (0.03 mole) of β -chloro

propionaldehyde diethyl acetal (Aldrich) was added at a rate of 1 drop per minute. After the addition was completed the mixture was stirred at -23°C for 24 hours and then an additional 24 hours at 0°C . A few ml of water were added and the tetrahydrofuran removed in vacuo. Water was added to the remaining oil and extracted with several 50 ml pentane extractions. The combined pentane extractions were washed with 10% KOH, then dried over anhydrous potassium carbonate. The oil which remained was distilled and found to contain only starting materials.

Carrying out the reaction under nitrogen and varying the temperature from 35°C to 78°C for 8 days did not alter the results.

1,1-diethoxy-2-bromopropane 24³⁷

A mixture of 13.5g (.11 mole) 1,1-diethoxyethane 7g calcium carbonate and 25 ml of carbon tetrachloride was placed in a round bottomed flask equipped with a mechanical stirrer. The reaction flask was kept in an ice bath as 20g of bromine were added from a dropping funnel. After the addition of bromine was complete (3 hours), the mixture was stirred for 2 hours after which water was added to dissolve the solid salts. The oil which appeared was separated, taken up in ether and dried over potassium carbonate. The ether was removed in vacuo and the remaining crude products vacuum distilled to yield 14.97g (70%).

colourless oil, b.p. 45-46°C (2.8mm); (lit.³⁷ b.p. 48-49/3mm).
 $n_D^{24} = 1.4377$; IR. 1380, 1350, 1115, 1065, 540, 528 cm⁻¹; nmr
 (CDCl₃) 4.6-4.8 (H, t, J=6), 3.3-3.5 (CH₂, d, J=5), 1.1-1.3
 (CH₃, t, J=8).

2-methyl-2-(2,2-diethoxyethane)-1,3-dithiane.

To a 3-necked round bottomed flask equipped with a mechanical stirrer was added 4.02g (.03 mole) of 2-methyl-1,3-dithiane and 100 ml of tetrahydrofuran. The mixture was cooled to -28°C (Dry Ice/CCl₄) and stirred under a nitrogen atmosphere as 1.05 equivalents of n-butyllithium solution in n-hexane (Foote Mineral Co.) was added. The bromide (0.03 mole) was then added to the solution which turned blue-green. The colour turned yellow after about 8 hours. The cooled mixture was stirred for three days to ensure reaction completion. To the solution 15ml of water were added, followed by separation of the organic layer to which was added 100ml of pentane. The pentane solution was washed with 50ml 10% aqueous potassium carbonate. The solvent was removed in vacuo and the remaining oil distilled to yield 10.5g (42%) of colourless product; b.p. 115-118°C (0.2-0.3mm);
 nmr (CDCl₃). 1.0-1.33 (CH₃, t, J=7-8), 1.54 (CH₃, s) 2.25-2.32 (CH₂, d, J=5), 3.30-3.66 (CH₂, q, J=6), 4.50-4.66 (H, t, J=4-5).

1,3-dithiane 22

The 1,3-dithiane was prepared according to the method outlined by Corey²³. The procedure gave 80% yield of white

crystals m.p. 52-53°C (lit.²³ 53-54°C); IR (CHCl₃) 1430, 1180, 920cm⁻¹; nmr (CDCl₃), 3.83(SCH₂S, s) 2.87(SCH₂, t), 1.9-2.3(CH₂m 2-(3,3-diethoxypropane)-1,3-dithiane 23

To 150ml tetrahydrofuran in a 250ml round bottomed flask was added 6g (0.05 mole) of 1,3-dithiane. The mixture was cooled to -23°C and stirred under a nitrogen atmosphere as 1.05 equivalents of n-butyl lithium solution in hexane was added dropwise over a period of 2 hours. To the cooled solution β -chloropropionaldehyde diethylacetal was added dropwise. The reaction mixture was kept at -23°C for one day then at 0°C for 2 more days. Finally, the mixture was stirred for 1 day at room temperature, after which time 30ml of water were added. The solution was extracted with four 100ml portions of pentane. The pentane extractions were combined and washed with a 10% KOH solution followed by two 75ml water washes. The pentane layer was then dried over anhydrous potassium carbonate and then vacuum distilled. Only two components were isolated. Spectra of the two fractions were identical in all respects with the starting materials.

5,5-dimethoxy-2-pentanone 9

A mixture of 63g of 2-methylfuran in 350ml of methanol was refluxed for 48 hours over 9g of Rexyn 100 (Fisher) cation exchange resin. The sodium salt of the resin did not produce any product, so the resin was used in the acid form.

The resin was held in a porous cup above the mixture. The reaction was completed, the solvent was removed in vacuo and the crude product distilled to yield 5-10g (5-10%) of colourless liquid b.p. 70-71°C (9mm) $n_D^{24} = 1.4200$ (lit. b.p. 85-87 at 15mm. $n_D^{25} = 1.4213$). nmr ($CDCl_3$) 4.2-4.4 (H, t, $J=5$), 3.25 (CH_3 , s), 2.11 (CH_3 , s); IR (CCl_4), 1728, 1365, 1075, 965 cm^{-1} .

4-chlorocyclohexanol 27

1,4-cyclohexanediol 100g (.43 mole) was treated with 100 ml concentrated HCl and heated to 100°C for 3½ hours. The reaction mixture was then poured into 200g of ice, followed by neutralization with sodium bicarbonate. Three 100ml portions of ether were used to extract the chloroalcohol. The ether extracts were concentrated, and then vacuum distilled to yield 28% of isomeric mixture of the 4-chlorocyclohexanol; b.p. 118-120°C at 18mm; 110-111 at 16mm, $n_D^{22} = 1.4949$, (lit. $n_D^{39} = 1.4930$), IR (CCl_4), 3360, 2940, 2860, 1445, 1250, 1058, 959, 945 cm^{-1} ; nmr (CCl_4), 1.2-2.5 (CH_2 , m), 3.5-4.4 (CH, m), 4.0 (OH, s).

4-chlorocyclohexyl acetate 29

A mixture of 10g (.086 mole) of 4-chlorocyclohexanol 100ml of pyridine, and 40g acetic anhydride was allowed to stir overnight. The reaction mixture was poured into 300ml of ice water. The oil which separated was extracted with ether and the ether layer washed with three 100ml portions

of 2% aqueous HCl solution, and once with water, after which the ethereal solution was dried over sodium sulfate and concentrated under vacuum. The crude product yield was 73.3% as analysed by v.p.c.. (8ft, 10% silicone gum rubber column, 3/8" O.D. at 135°C, 1cc/sec). Some product was collected by gas chromatography, $n_D^{24} = 1.4640$ (lit. $n_D^{39} = 1.4659$); $D_4^{19} = 1.1282$; b.p. 111-112°C, (18mm). IR (CHCl₃), 1735, 1380, 1370, 1260, 1050, 665 cm⁻¹, nmr (CDCl₃), 4.8 (CH), 2.07 (CH₃, s).

4-bromocyclohexanol

A mixture of 23.2g (0.20 mole) of 1,4-cyclohexanediol and 17ml (.20 mole) of concentrated HBr was heated for 2 hours at 110°C. The hot solution was poured into 100g of ice, neutralized with sodium bicarbonate, saturated with sodium chloride and extracted with three 100ml portions of ether. The combined ether extracts were dried over sodium sulfate and concentrated in vacuo. The crude product was vacuum distilled to yield 7.8g (23%) of alcohol; b.p. 90°C (9.3mm), (lit. n_D^{39} b.p. 113°C (15mm)); IR, 3420, 2957, 2875, 1455, 1247, 1060, 965 cm⁻¹; nmr (CDCl₃), 1.1-2.5 (CH₂, m), 2.6 (OH, s), 3.5-4.7 (CH, m).

4-chlorocyclohexanone 28

The ketone was prepared by the oxidation of 4-chlorocyclohexanol using the Jones reagent³⁶. The reagent was made up as 26.7g CrO₃, 23ml conc. H₂SO₄ and 75 ml of water. To 10.4g (0.07 mole) of alcohol dissolved in 100ml of acetone, 21.2ml (1.2 equivalents) of the prepared reagent were

added dropwise from a burette, for a period of 2 hours. During the addition, the acetone solution was kept at -20°C (Dry Ice/ CCl_4). The organic layer was separated and combined with the ether washings of the inorganic layer. The combined extracts were washed with sodium bicarbonate, dried with anhydrous sodium sulphate, and vacuum distilled to yield 74% of the ketone 28; b.p. $100-102^{\circ}\text{C}$ at 18mm (lit.³⁸ 95°C 17mm) IR; 2970, 1720, 1440, 1327, 1258, 1240, 1131cm^{-1} ; nmr (CCl_4) 2.15-2.70 (CH_2 , m), 4.5 (CH, q)

The semicarbazone (m.p. $193-194^{\circ}\text{C}$; lit.³⁸ 191°C) and 2,4-dinitrophenylhydrazine (m.p. $126-127^{\circ}\text{C}$) were prepared as derivatives.

4-chlorocyclohexyl ethylene ketal 8

The ketal was prepared by reacting 6.4g (.003 mole) of the 4-chlorocyclohexanone with 25g (.40 mole) of ethylene glycol in 75ml of sodium dried toluene. A catalytic amount of *p*-toluenesulphonyl chloride was added. The toluene was slowly distilled off as fresh (sodium dried) toluene was added. A total of 200ml of toluene was collected. The ketal was found in the toluene layer although there were traces in the glycol layer. After the toluene layer was separated, the solvent was removed leaving a yellow oil which was found to contain 84% ketal 8 (v.p.c.). The ketal was purified by vacuum distillation in 85% yield; b.p. $110-111^{\circ}\text{C}$ at 15mm, $225-232^{\circ}\text{C}$ at 760mm; $n_D^{25}=1.4920$; IR; 2963, 1370, 1262, 1110.

1035 cm^{-1} ; nmr (CDCl_3) 1.5-2.3 (CH_2 , m), 3.9 (OCH_2 , s), 4.0-4.3 (CH, m).

Reaction between triphenylphosphine and 8

To 50ml of toluene was added 8.1g (.05 mole) of the chloroketal 8 and 11g (.05 mole) of triphenylphosphine. The mixture was refluxed for 15 hours after which time no precipitate had formed. The solvent was changed to xylene and the reaction mixture again was refluxed for 15 hours, after which time no salt had formed. The xylene was removed and the reagents heated neat (190-200°C). After 12 hours the reaction mixture was cooled. The solid present was filtered off and washed several times with ether. The salt was then recrystallized from chloroform/ethylacetate (1:1). The white salt was obtained in 45% yield; m.p. 265-270°C; IR; 1590, 1485, 1440, 1245, 1110, 910 cm^{-1} ; nmr (CDCl_3), 4.12-4.5 (2H, m), 7.5-8.5 (15H, m).

The absence of cyclohexyl protons indicated this salt could not be the desired product.

Reaction between triphenylphosphine and 29

A mixture of .7g (.0004 mole) of the acetate, and 1.1g (.0004 mole) of triphenylphosphine was heated without solvent for 4 days. The reaction mixture was then cooled, and 5ml of ether added. The solid which was ether insoluble was filtered off and washed with cold ether. This solid (.7g) was characterized as triphenylphosphine oxide; m.p. 148-

150°C, IR, 2995, 1600, 1440, ..80, 1120, 550cm⁻¹; nmr (CHCl₃), 7.5-8.5 (m).

Reaction of 8 with lithium metal

This reaction was conducted in a sealed nmr tube in an attempt to follow the formation of the product. A mixture of ether, lithium metal and the chloride 8 were heated to 30°C for 20 minutes. After this time, there was no reaction between the chloride and the lithium metal. The mixture was allowed to stand for two weeks at room temperature, after which time still no reaction had taken place.

Reaction of 34 with 1,1-dimethoxy-4-pentanone

The Grignard reagent was prepared by refluxing 12.3g (.07 mole) of the chloride 8 with 2.1g (.09 mole) magnesium turnings in 100ml of tetrahydrofuran for a period of 2 hours. During the refluxing period an aliquot of the reagent 34 was added to the water, extracted with chloroform, and dried over potassium carbonate. An IR was then taken; 3500, 1450, 1375, 1265, 1223, 1100cm⁻¹). To the reagent was added 15.6g (0.1 mole) of the ketone 9. The solution was stirred for 30 minutes and then poured into a beaker containing a saturated ammonium chloride solution. The organic layer was extracted with three portions (100ml) of ether which were dried over anhydrous potassium carbonate. The solvent was evaporated and an oil remained (21.7g). Excess ketone 9 was distilled off, but prolonged heating of the "pot" was

avoided to prevent dehydration. The oil which remained was found to have a total of ten components (v.p.c.- 10 ft., 1/4 in. O.D., 20% SE.30) of which three components accounted for 50% of the products. Dehydration of the alcohol on the chromatographic column may have occurred to give these three peaks. The nmr integration indicates the pot mixture consists of 60% product. The overall yield of alcohol 35 was 34%; IR(CCl₄) 3500, 2950, 2880, 1445, 1375, 1365, 1190, 1130, 1110cm⁻¹; nmr (CDCl₃) 1.07 (CH₃, s), 1.0-2.8 (CH₂, m), 3.3(OCH₃, s), 3.9 (OCH₂, s), 4.3 (CH, t).

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VITA AUCTORIS

- Born - September 21, 1948 - Montreal, Quebec
- Son of Mr. and Mrs. Germain Beaumier
- Primary School - Holy Cross School, Montreal, Quebec
- Secondary School - St. Thomas Aquinas High School, Montreal
Quebec
- University - Loyola Of Montreal, Montreal, Quebec 1965-1969
- Degree - Bachelor of Science in Honours Chemistry
- University of Windsor, Windsor, Ontario 1969-1972
Graduate Research and Teaching Assistant
- Publications - Improved preparation of 1, 3-cyclopentanedione,
J. Org. Chem. 37, 2905 (1972)
- The Alkylation of Cyclic Diketone Thallium (I)
Salts, Can. J. Chem. 51, 843 (1973)
- Marital Status - Married June 17, 1972, to Colleen Churcott